Summary of Research Activities by Disease Category

Infectious Diseases and Biodefense

In April 2009, a new strain of the influenza virus emerged in Mexico and quickly spread around the globe. Because of its experience responding rapidly to emerging disease threats, NIH was poised to quickly mount a major research effort to learn about this new virus strain and to develop approaches to reduce its impact on public health. The virus now is known as 2009 H1N1 influenza A. Building on a strong foundation of basic research on influenza viruses, NIH was engaged fully in the government-wide effort to understand the biology of the 2009 H1N1 influenza virus and its interaction with humans, and to rapidly develop effective vaccines and therapies. NIH used its longstanding vaccine clinical trials infrastructure to quickly evaluate pilot lots of vaccine candidates to determine their safety and ability to induce protective immune responses, and to ascertain the appropriate dose and number of doses needed for immunization. NIH-supported trials included studies of specific populations, such as pregnant women, children, HIV-infected individuals, and people with asthma, along with trials of healthy adults and elderly. This information was crucial in informing the establishment of public health guidelines for H1N1 vaccines. By conducting essential research, and by establishing effective partnerships with international agencies, other Federal agencies, and private industry, NIH was instrumental in the effort to prepare a 2009 H1N1 influenza vaccine in time for the fall 2009 Northern Hemisphere flu season.

Introduction

The goals of NIH-supported research on infectious diseases and biodefense rest on two core components. NIH builds and maintains a base of fundamental knowledge about infectious and immune-related diseases and uses that knowledge to develop new and improved diagnostics, therapeutics, and preventive measures, including vaccines. At the same time, NIH continues to develop a flexible domestic and international infrastructure that allows it to respond to newly emerging and re-emerging threats wherever they occur, thereby protecting public health in the United States and abroad.

Infectious Diseases

Infectious diseases are caused by microbial pathogens—bacteria, viruses, fungi, protozoa, and helminths (worms)—that invade the body and multiply, causing physiological damage and illness. Pathogens cause a range of diseases from minor to life-threatening and can be transmitted in many ways. Influenza and tuberculosis (TB) can be transmitted from person to person via airborne inhalation; HIV, which causes AIDS, is transmitted through exposure to blood or other body fluids; and malaria is caused by a microscopic parasite that is transmitted by an insect "vector," in this case a mosquito. Transmissible infectious diseases can devastate large human populations rapidly and easily cross international borders.

Biodefense and Emerging and Re-emerging Infectious Diseases

Public health threats that could cause large-scale disruption and devastation include the deliberate or accidental release of pathogenic agents such as anthrax or smallpox, biological toxins, chemical weapons such as nerve gas, or radioactive substances. Threats to public health change continually as new pathogens emerge, and as familiar microbes reemerge with new properties or in unusual settings.

The NIH biodefense strategy integrates basic, applied, and clinical research knowledge and capabilities into a flexible and adaptable approach designed to create interventions that target single as well as multiple pathogens. Examples of recent emerging and re-emerging public health threats include naturally occurring infectious diseases such as 2009 H1N1 and H5N1 influenza, Ebola hemorrhagic fever, and severe acute respiratory syndrome (SARS). The overall goal of research on biodefense and emerging and re-emerging infectious diseases is to develop the knowledge and tools to respond quickly and effectively as public health threats emerge, whether they occur naturally, accidentally, or deliberately.

Although NIAID has primary responsibility for infectious diseases and biodefense research, many other NIH ICs play critical roles, including FIC, NICHD, NIEHS, NINDS, and OAR. All of the NIH ICs support AIDS-related research activities, consistent with their individual missions. The ICs that conduct most of the research on AIDS and its associated co-infections, malignancies, cardiovascular and metabolic complications, and behavioral and social science issues are NIAID, NIDA, NCI, NIMH, NCRR, NICHD, and NHLBI. All NIH AIDS research is coordinated by OAR.

In addition, the NIH Office of Science Policy manages and supports the National Science Advisory Board for Biosecurity (NSABB). Taking into consideration national security concerns and the needs of the research community, the NSABB provides advice on strategies for the efficient and effective oversight of dual-use biological research—research that has a legitimate scientific purpose but if misused could pose a threat to public health or national security (also see the section on *Ensuring Responsible Research* in Chapter 1).

NIH-wide research on infectious diseases and biodefense includes basic research to understand fundamental mechanisms by which microorganisms cause disease, the host response to pathogens, and mechanisms by which insects and other vectors transmit infectious diseases. Translational research builds on basic research findings with the aim of developing new and improved diagnostics, therapeutics, vaccines, and other preventive measures. NIH conducts and supports clinical research to assess the efficacy and safety of candidate drugs, vaccines, and other products. As NIH pursues these goals, an overarching priority is to reduce health disparities and improve health for all people.

Infectious diseases and biodefense inherently are global concerns. NIH engages in international partnerships to improve means for detecting and controlling the spread of infectious diseases and supports international programs to foster research and research capacity in developing countries. Within the United States, NIH seeks strategic partnerships with other governmental and nongovernmental organizations.

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NIH supports research on HIV/AIDS, TB, malaria, emerging and re-emerging infectious diseases (such as hemorrhagic fevers caused by Ebola and other viruses, West Nile virus, SARS, Lyme disease, prion diseases, and H5N1 [a virus that causes avian influenza]), sexually transmitted infections, and influenza and other respiratory infections. In addition, NIH funds research on many less familiar but still important diseases that exact an enormous global toll.[28]

NIH research on biodefense and emerging and re-emerging infectious diseases necessarily is intertwined and includes the development of infrastructure and capacity-building, that is, facilities and human resources needed to conduct research on dangerous pathogens safely and effectively; basic research on microbes and host immune defenses; the targeted development of medical countermeasures, including vaccines, therapeutics, and diagnostics; and training for emergency and

skilled workers that would be needed in the event of a biological, chemical, or radiological weapons attack or other public health emergency.

[28] For more information, see http://www3.niaid.nih.gov/topics/BiodefenseRelated/default.htm

Burden of Illness and Related Health Statistics

Infectious diseases cause approximately 26 percent of all deaths worldwide. Each year, more than 11 million people die from infectious diseases; the vast majority of deaths occur in low- and middle-income countries. The top infectious disease killers in those countries for people ages 15 to 59 are HIV/AIDS, TB, and lower respiratory infections.[29] Worldwide, HIV causes nearly 2.0 million total deaths each year,[30] TB kills 1.6 million each year,[31] and lower respiratory infections in 2005 caused an estimated 3.7 million deaths.[32] Malaria is a serious problem, especially in Africa, where one in every five childhood deaths is due to the effects of the disease.[33] The infectious diseases that today cause the greatest number of human deaths worldwide are (in order) lower respiratory infections, HIV/AIDS, diarrheal diseases, malaria, and TB.[34]

Each year infectious diseases kill approximately 6.5 million children, most of whom live in developing countries. For children younger than age 14, infectious diseases account for 7 of the top 10 causes of death. In this age group, the leading infectious diseases are lower respiratory infections, diarrheal diseases, and malaria. Among children younger than age 5, infectious diseases cause about two-thirds of all deaths.[35]

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The burden of infectious diseases is not evenly shared, even among developing nations. People who live in sub-Saharan Africa are most affected, particularly by HIV/AIDS, which accounts for one in five deaths in that region. Africa and the most populous countries of Asia harbor the largest number of TB cases. Together, Bangladesh, China, India, Indonesia, and Pakistan account for half of new TB cases each year.[36]

In the United States, infectious diseases add significantly to the overall burden of illness. Together, influenza and pneumonia account for more than 56,000 deaths annually.[37] More than a million cases of sexually transmitted diseases occur each year, including 56,400 new HIV infections, and more than 37,000 new cases of AIDS were reported in 2007.[38]

Also, many infectious diseases increasingly are difficult to treat because pathogens are developing resistance to antimicrobial drugs. For example, in recent years there have been dramatic increases in antiretroviral drug resistance in HIV, chloroquine resistance in malaria, the emergence of multidrug-resistant TB (MDR TB) and extensively drug-resistant TB (XDR TB), and methicillin-resistant *Staphylococcus aureus* (MRSA) infection.

[29] For more information, see WHO *Disease Control Priorities Project* Infectious Diseases chapter (April 2006), http://www.dcp2.org/file/6/DCPP-InfectiousDiseases.pdf.

[30] For more information on the global HIV/AIDS pandemic, see http://www.unaids.org/en/KnowledgeCentre/HIVData/EpiUpdate/EpiUpdArchive/2009/2009epidemic_update.asp.
[31] For more information on tuberculosis, see http://www3.niaid.nih.gov/topics/tuberculosis.
[32] For more information, see http://www.who.int/entity/mediacentre/factsheets/fs310.pdf.
[33] For more information, see http://www.who.int/features/factfiles/malaria/en/index.html.
[34] For more information, see *Global Burden of Disease and Risk Factors*. Eds. Lopez AP, et al. Oxford University Press and the World Bank. 2006. Available at http://files.dcp2.org/pdf/GBD/GBDFM.pdf.
[35] For more information, see WHO *Disease Control Priorities Project*, Infectious Diseases chapter (April 2006), see http://www.dcp2.org/file/6/DCPP-InfectiousDiseases.pdf.
[36] For more information, see http://www.dcp2.org/main/Home.html.
[37] For more information, see http://www.cdc.gov/nchs/fastats/deaths.htm.
[38] CDC Cases of HIV Infection and AIDS in the United States and Dependent Areas, by Race/Ethnicity, 2003—2007, Table 4. See http://www.cdc.gov/hiv/topics/surveillance/resources/reports/2009supp_vol14no2/table4.htm.

NIH Funding for Infectious Diseases and Biodefense Research

Actual NIH funding support levels for infectious diseases research were $3,575 million in FY 2008, and $3,627 million and $526 million in FY 2009, respectively, for non-ARRA (regular appropriations) and ARRA (Recovery Act appropriations). Actual funding levels for biodefense research were $1,736 million in FY 2008, and $1,746 million and $213 million in FY 2009, respectively, for non-ARRA and ARRA. There is substantial overlap between the funding figures for infectious diseases research and biodefense research. Click on the funding levels, which are live links, to produce detailed project listings. These lists are derived from the NIH Research, Condition, and Disease Categorization (RCDC) system. In addition, the table at the end of this chapter indicates some of the research areas involved in these investments (see *Estimates of Funding for Various Research, Condition, and Disease Categories*).

Summary of NIH Activities

NIH programs on infectious diseases and biodefense encompass a broad portfolio of basic, translational, preclinical, and clinical research. These activities include developing critical infrastructure and research resources, and providing training to develop scientific expertise in the United States and abroad. These activities allow NIH to mount an effective research response to public health threats wherever they occur.

Basic Research

NIH basic research on infectious diseases and biodefense seeks to illuminate the fundamental biology and interactions of pathogens and hosts. The knowledge gained provides the foundation for improvements in prevention, diagnosis, and treatment of infectious diseases and contributes to our country's preparedness against the threat of bioterrorism as well as naturally occurring disease outbreaks. Basic research spans topics from genes to global climate change to the use of technologies such as bioinformatics, proteomics, and systems biology to evaluate pathogens.

In its intramural and extramural programs, NIH conducts and supports genome sequencing of pathogens and hosts that helps reveal how microbes evolve, infect host cells, cause disease, develop drug resistance, and spread. As patterns of disease transmission reflect the impact of environmental changes, NIH-supported researchers seek to identify the mechanisms by which insects and other vectors transmit infectious disease.[39] On a global level, researchers pursue interdisciplinary research

to decipher the underlying ecological and biological mechanisms that govern relationships between human-induced environmental changes and the emergence and transmission of infectious diseases[40] including influenza, malaria, and dengue.

An important facet of NIH-supported research is the effort to expand understanding of human immune responses. The Adjuvant Development Program, launched in 2008, builds on the successful Innate Immune Receptors and Adjuvant Discovery Program. The goal is to identify existing adjuvants—substances added to stimulate or boost an immune response—that could be licensed for human use in vaccines against infectious agents such as influenza, TB, and West Nile virus. In 2008, researchers found that the adjuvant alum activates the innate immune system by stimulating clusters of proteins called inflammasomes, found inside certain cells.[41] This finding enhances understanding of adjuvant function and may facilitate the design of new adjuvants.

The Adjuvant Development Program, launched in 2008, aims to identify substances that can be added to vaccines to boost immune responses to infectious agents such as influenza, TB, and West Nile virus.

NIH also is intensifying its focus on primary immune deficiency diseases (PIDD), which dramatically increase susceptibility to infections. In 2007, NIH opened the Primary Immune Deficiency (PID) Clinic on the NIH campus. PID Clinic scientists reported that a mutation in the gene *DOCK8* might underlie a newly identified category of PIDD, tentatively called DOCK8 immunodeficiency syndrome.

Other basic research seeks to understand how complex, multichain sugar molecules called oligosaccharides might act as antimicrobial agents that help prevent bacterial and viral infections of the digestive tract.[42] These oligosaccharides are present in human milk, but are non-nutritive, raising the question of why they persist in evolution. The research could lead to novel approaches for synthesizing antimicrobial oligosaccharides to treat people who have been exposed to gastrointestinal pathogens.

Basic research initiatives launched in 2009 focus on investigating the linkages between malnutrition and intestinal infections and their effects on children in the developing world;[43] supporting a program to build on recent advances in immune profiling to measure the diversity of human immune responses to infection or vaccination; discovering how the lung microbiome—the mix of microorganisms that inhabit the respiratory tract—might increase the likelihood of severe respiratory problems in people infected with HIV;[44] and advancing understanding of the risks, development, progression, diagnosis, and treatment of malignancies—including hepatocellular carcinoma—in individuals with underlying HIV infection or AIDS.

Research on the causes of antimicrobial resistance (such as how bacteria develop and share resistance genes) explores how disease-causing bacteria such as MRSA and vancomycin-resistant *S. aureus* (VRSA) develop resistance to previously effective antibiotics.[45] NIH is conducting clinical tests to evaluate the efficacy of off-patent antimicrobial agents as possible interventions for the effective treatment of hospital-acquired MRSA infection.

Research on the causes of antimicrobial resistance (such as how bacteria develop and share resistance genes) explores how disease-causing bacteria such as methicillin-resistant S. aureus (MRSA) and vancomycin-resistant S. aureus (VRSA) develop resistance to previously effective antibiotics.

NIH basic and translational research includes studies using animal models to determine how bone

marrow stromal cells, which help modulate immune responses, might be used to treat sepsis, the widespread activation of inflammation and blood clotting pathways that can accompany a severe infection and lead to multiple organ failure, septic shock, and death.[46]

[39] For information about the Vector Biology Research Program, see http://www3.niaid.nih.gov/topics/vector/.
[40] For information about funding for research through the NIH Evolution of Infectious Diseases Program, see http://grants.nih.gov/grants/guide/pa-files/PA-07-130.html. See also Rosenthal JP, Jessup CM. *Trans Am Clin Climatol Assoc* 2009;120:129-41. PMID: 19768170. PMCID: PMC2744516.
[41] For more information, see http://www3.niaid.nih.gov/news/newsreleases/2008/alum_vaccine.htm.
[42] For information about NIH funding for research on antimicrobial and prebiotic activity of oligosaccharides, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-08-004.html.
[43] For more information, see http://origem.info/malnutritionstudy/.
[44] For information about NIH funding for research on the lung microbiome, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-09-006.html.
[45] For more information, see http://www3.niaid.nih.gov/topics/AntimicrobialResistance/default.htm.
[46] Németh K, et al. *Nat Med* 2009;15(1):42-9. PMID: 19098906. PMCID: PMC2706487.

Major Infectious Diseases

NIH conducts research on hundreds of infectious diseases, with special emphasis on those that claim large numbers of lives each year. Research includes studies of major infectious diseases such as TB, malaria, and HIV/AIDS, as well as studies to ensure the health of special populations—individuals whose immune systems are compromised, the elderly, adolescents, young children, and infants. NIH also explores how human behaviors as well as social, cultural, economic, and geographic factors affect disease transmission. The ultimate goal is to translate knowledge gained through basic research into interventions that improve public health in the United States and other countries.

Tuberculosis

TB, an ancient disease, remains one of the major causes of disability and death worldwide. It also is a prototypical example of a re-emerging disease, due to the HIV/AIDS co-epidemic and an increase in the prevalence of drug-resistant forms of the bacillus *Mycobacterium tuberculosis* (*Mtb*) that are much more difficult to treat. Persons co-infected with HIV often have weakened immune systems and are much more likely to develop active TB disease after infection with *Mtb*. HIV co-infection increases the risk of developing active TB by a factor of 20 or more.[47]

NIH continuously is expanding its TB research program using state-of-the-art technologies to develop new tools for rapid, early diagnosis; new vaccines to prevent TB; and improved therapies for all forms of the disease, including drugs for MDR TB and XDR TB. Researchers are working to understand the basic biology and immunology of TB; improve clinical management of MDR TB and XDR TB in people with and without HIV infection, including children; and prevent TB by various means, including vaccines.[48]

Some of this research already has borne fruit. Investigators found that two FDA-approved drugs, meropenem and clavulanate—used to treat other bacterial diseases—work in tandem to kill *Mtb* in laboratory models.[49] A clinical trial is being developed to test the combination in people who have drug-resistant TB.[50] Also, NIH-supported clinical trials showed that mortality among persons with TB who are co-infected with HIV drops markedly when they receive antiretroviral (ARV) therapy and TB

therapy concurrently.

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To address problems related to TB in countries with high burden of disease, NIH is increasing its focus on persons who also are afflicted with other diseases and conditions, such as HIV, diabetes, and malnutrition.[51]

[47] For more information, see http://www.who.int/tb/publications/global_report/2009/en/index.html.
[48] For more information, see http://www3.niaid.nih.gov/topics/tuberculosis.
[49] Hugonnet JE, et al. *Science* 2009;323(5918):1215-8. PMID: 19251630. PMCID: PMC2679150.
[50] For more information, see http://www3.niaid.nih.gov/news/newsreleases/2009/TB_drug_combo.htm
[51] For more information, see http://www3.niaid.nih.gov/topics/tuberculosis/Research/NIAIDsRole.htm.

Malaria

Malaria continues to exact a devastating toll on individuals worldwide, mostly among children in sub-Saharan Africa. Approximately half of the world's population lives in regions at some risk for malaria. Achieving the ultimate goal of ridding malaria from every region of the globe will require three phases: control, elimination and, finally, eradication.

In 2009, NIH joined the Roll Back Malaria (RBM) Partnership in an intensified effort to halve the global malaria burden by 2010, an important milestone on the road to achieving the WHO Millennium Development Goal of reducing malaria deaths to near zero by 2015. NIH supports research on 10 candidate vaccines for malaria, 5 of which are in clinical trials. Researchers studying basic mosquito biology recently identified genetic markers involved in pyrethroid insecticide resistance; these now are being evaluated for utility in the field.

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A recently launched NIH initiative, the International Centers of Excellence in Malaria Research, supports a global, multidisciplinary approach to understanding malaria in the context of control, elimination, and eradication. Outstanding needs include faster and more reliable ways to diagnose malaria and to identify different parasite species and drug-resistant strains that may emerge, systematic methods for translating basic research into effective treatment and control strategies, and safe and effective therapies to counteract strains of the malaria parasite that have developed resistance to current drugs.

HIV/AIDS

HIV/AIDS continues to devastate communities around the world. Without a vaccine to protect against

HIV infection or a cure for HIV/AIDS, new biomedical approaches and behavioral interventions urgently are needed to stop the HIV/AIDS pandemic. NIH conducts and supports research to develop new strategies and methods that prevent the spread of HIV, such as vaccines, microbicides, strategies to prevent mother-to-child transmission, antiretroviral therapy (ART) as a pre-exposure prophylaxis strategy, treatment for drug addiction, and behavioral interventions. The goal of the NIH prevention research agenda is to develop a "toolbox" of scientifically proven prevention strategies that can be tailored to different populations affected by HIV/AIDS around the world.

The ultimate prevention tool—and what is considered the best hope for ending the HIV/AIDS pandemic—is a safe and effective vaccine that can prevent HIV infection. NIH recently renewed its emphasis on basic research in HIV vaccines through two major initiatives.[52] The Basic HIV Vaccine Discovery Research Program, which began in 2008, seeks to generate knowledge to inform new conceptual designs and approaches to HIV vaccines. Through the B Cell Immunology for Protective HIV-1 Vaccine Program, NIH fosters basic immunology research on B cell and antibody regulation as a foundation for the development of new HIV vaccines. In addition, NIH recently launched an exploratory clinical trial through the HIV Vaccine Trials Network (HVTN) to examine whether a two-part vaccine regimen can decrease viral load in vaccinated male study participants who later become infected with HIV.

NIH also is advancing other new approaches in HIV prevention. Two NIH-supported trials recently showed that medically supervised circumcision of adult males markedly reduces the risk of acquiring HIV infection, and that the microbicide gel PRO 2000 was safe and potentially effective in women.[53] Additional studies are evaluating other microbicides—gels, creams, or foams applied to the vagina or rectum—that are designed to prevent HIV and other sexually transmitted infections. Through collaborations with government and nongovernmental partners, NIH also is evaluating an HIV prevention strategy called pre-exposure prophylaxis (PrEP), which involves providing ARV drugs to HIV-negative individuals who are at high risk of HIV infection.[54] Additionally, recent modeling data have shown that universal voluntary, routine HIV testing and immediate treatment of individuals diagnosed with HIV could reduce dramatically the number of new HIV cases in the next decade. This approach is based on the premise that immediate initiation of ARV therapy for those individuals who test positive would lower their viral load in the blood and, thereby, reduce the spread of HIV. NIH is addressing critical research questions to determine the feasibility of this "test and treat" approach.[55]

Aging is an expanding focus of HIV/AIDS research at NIH. HIV/AIDS began its deadly course in the United States mostly as a disease of young men. Today, due to a growing number of cases newly diagnosed in older persons and the advent of potent, multidrug therapy against HIV in the mid 1990s, many HIV-infected Americans are living into their 50s and well beyond. Older adults with long-term or new HIV infection experience complex interactions among HIV, antiretroviral therapy (ART), age-related changes to the body, and, often, treatment for illnesses associated with aging.

NIH supports research on the interaction between HIV and aging in areas as diverse as organ diseases, cancer, bone density, mental health, response to antiretroviral therapy, and immune function. For example, researchers with the Multicenter AIDS Cohort Study (MACS) have shown that HIV infection accelerates the development of frailty, a condition of the elderly that makes people more vulnerable to illness, injury, and death. Scientists now want to determine which HIV-infected individuals are at highest risk for developing HIV-associated frailty, with the hope of identifying factors to mitigate or prevent its development. Individuals who undergo long-term ART frequently experience side effects of disease and treatment that mimic or accelerate aging processes. NIH supports efforts to evaluate emerging issues in HIV clinical care such as the impact of aging on HIV treatment response.[56] NIH recently established a multi-Institute collaboration to solicit research on clinical and translational medical issues in the diagnosis and/or management of HIV infection and its consequences in older people[57] and initiated a prospective study to identify possible long-term adverse outcomes of HIV infection and complications of ART or experimental interventions in HIV-infected

infants, children, and adolescents.

NIH also is expanding its efforts to find a cure for HIV/AIDS. Through research to improve basic understanding of HIV latency, NIH seeks to achieve long-term HIV remission following discontinuation of ARV therapy—a "functional" cure—or, ultimately, complete eradication of residual virus. NIH supports research to eliminate HIV reservoirs, pockets of undetectable latent and persistent HIV, which exist even in people on ARV therapy who have an undetectable viral load.

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To ensure that vulnerable populations benefit from research progress on HIV/AIDS, NIH has launched initiatives to reduce HIV transmission, ensure access to rapid screening tests, and deliver effective treatment. An initiative begun in 2008, HIV Rapid Testing and Counseling in Drug Abuse Treatment Programs in the United States, explores new avenues to prevent and treat HIV disease among drug users. Outreach programs among drug users have helped to reduce HIV/AIDS transmission. NIH also is working to ensure that effective HIV/AIDS treatment reaches the prison population and that inmates, once released, continue to receive effective treatment.[58] A study to determine whether intervention helps reduce risky sexual behaviors among homeless HIV-positive adults indicates that intervention programs focusing on skills development and the physical and mental health needs of participants are more likely to succeed than are programs focused only on reducing HIV transmission.[59] A recent Adolescent Medicine Trials Network for HIV/AIDS (ATN) study documented that HIV-positive adolescents frequently do not follow prescribed treatment regimens, and identified several factors associated with nonadherence to therapy.

NIH also supports initiatives to address the U.S. epidemic in specific racial and ethnic populations. NIH has launched a new initiative to address the serious and complex HIV/AIDS epidemic in U.S. Hispanic populations through community outreach, regional workshops, leadership development, and research collaborations.[60]

NIH is continuing its support of the two largest observational studies of HIV/AIDS in women (Women's Interagency HIV Study) and homosexual or bisexual men (MACS) in the United States.[61] Recent cohort studies focus on aging veterans[62] and more generally on aging, sleep disorders, frailty, renal function, cognitive function, and behavior among HIV-infected persons. NIH also supports two prospective cohort studies of HIV-infected women, HIV-exposed but uninfected children, and HIV-infected children at clinical sites in Latin America (the NICHD International Site Development Initiative Perinatal and Pediatric cohorts). In addition, the Pediatric HIV/AIDS Cohort Study (PHACS) includes an observational study of HIV infection among perinatally infected youth entering adolescence and young adulthood, as well as a study to evaluate the long-term effects of exposure to ARV drugs during gestation on uninfected infants born to HIV-infected mothers.

NIH disseminates research findings and other important information about HIV/AIDS through ***AIDS info*** and ***infoSIDA***, as well as a new initiative to incorporate information from AIDS-related conferences into the NLM Gateway service for public access on the Web.

[52] For more information, see http://www3.niaid.nih.gov/topics/HIVAIDS/Research/vaccines/research/.
[53] For more information, see http://www3.niaid.nih.gov/topics/HIVAIDS/Research/prevention/research/Microbicides/research.htm.
[54] For more information, see http://www.prepwatch.org/.

[55] For more information, see http://www3.niaid.nih.gov/news/newsreleases/2009/test_treat.htm.
[56] For more information, see http://statepiaps.jhsph.edu/naaccord/.
[57] For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-09-017.html.
[58] Baillargeon J, et al. *JAMA* 2009;301(8):848-57. PMID: 19244192; Chandler RK, et al. *JAMA* 2009;301(2):183-90. PMID: 19141766; PMCID: PMC2681083.
[59] For more information, see http://www.nimh.nih.gov/science-news/2008/intervention-helps-reduce-risky-sexual-behavior-among-homeless-hiv-positive-adults.shtml.
[60] For more information, see http://www.oar.nih.gov/strategicplan/fy2010/pdf/Chapter5.pdf.
[61] For more information, see http://www3.niaid.nih.gov/about/organization/daids/daidsepi.htm.
[62] For more information, see http://www.vacohort.org/.

Emerging Infectious Diseases and Biodefense (including seasonal and other influenzas)

NIH is the lead agency within HHS for conducting and supporting research on potential agents of bioterrorism and emerging infectious diseases that directly affect human health. NIH research to combat naturally occurring diseases overlaps with efforts to address threats posed by the accidental or intentional release of hazardous biological, chemical, or radiological agents. The overriding goal of these research programs is to enable NIH to respond effectively to a public health emergency regardless of its cause. In addition to basic, translational, and clinical research to develop safe and effective medical countermeasures, NIH supports programs to expand research infrastructure and maintain resources such as the Influenza Virus Resource.[63] Biodefense research includes the development of new and improved vaccines and therapeutics against smallpox, anthrax, botulinum toxin, and other potential bioterror agents.

The sudden and unpredictable appearance of 2009 H1N1 influenza is a classic example of an emerging infectious disease.[64] As of October 2009, more than 340,000 people worldwide had confirmed cases of 2009 H1N1 flu and more than 4,100 (1.2 percent) had died. NIH-funded researchers have discovered that the genes of the 2009 H1N1 influenza virus[65] are derived from human flu viruses, avian flu viruses, and swine flu viruses, including the H1N1 virus that caused the 1918 pandemic, which killed 40-50 million people worldwide. In collaboration with Centers for Disease Control and Prevention (CDC) scientists, NIH-funded researchers found that the 2009 H1N1 viruses replicate more efficiently in lung tissue than do seasonal flu viruses. NIH is conducting clinical trials of H1N1 vaccines in adults, children,[66] HIV positive women, and people with asthma, and has initiated the first clinical trial of an H1N1 influenza vaccine in pregnant women.[67]

NIH also is assessing the ability of experimental antiviral drugs to block infection with 2009 H1N1. Researchers are working to develop or refine antiviral drugs and diagnostic tools for both seasonal and pandemic influenza (2009 H1N1) strains. NIH is developing diagnostic platforms than can rapidly identify a wide variety of pathogens in clinical samples, including specific subtypes of influenza. Some of these diagnostics already are being used in clinical settings to help meet the increasing demand for rapid and accurate diagnosis of influenza, including the 2009 H1N1strain. NIH supports a diverse portfolio of basic influenza research with the ultimate goal of developing universal influenza vaccines that can protect against multiple strains of the virus.

Global demand for the 2009 H1N1 vaccine highlighted the urgency of developing new, faster, more efficient methods of vaccine production. Currently, influenza vaccines produced in the United States rely on egg-based manufacturing methods. Influenza vaccines have been prepared in eggs for years, but the process is lengthy and requires hundreds of millions of eggs. Cell culture-based vaccines currently are licensed only in Europe, and it may be some time before vaccines produced using cell cultures are licensed in the United States. NIH actively supports research to improve current influenza technologies and vaccines and develop new ones. Innovative vaccine technologies being developed by NIH and its industry partners include using recombinant DNA to create subunit vaccines in which various influenza virus proteins are selectively produced in cultured cells and are then purified and

used in a vaccine; DNA vaccines, in which influenza genetic sequences are used to stimulate an immune response against the proteins coded for by these genetic sequences; and approaches that insert the genes of influenza viruses into a different virus (a "vector") that is used as a vaccine. These and other "next generation" vaccines must undergo extensive development, safety, and efficacy testing before they can be used, and then will require time to reach commercial levels of manufacturing.

An important facet of preparedness for emerging infectious diseases is the need to protect health care workers. Many workers are at risk for exposure to emerging airborne biological agents, including the 2009 H1N1 influenza virus and other pandemic influenza viruses, *MTb*, and other viruses. Some hospital workers are exposed to accidental releases of hazardous biological materials due to lack of proper training, engineering controls, handling, storage, or poor maintenance and cleaning of laboratory equipment. With NIH support, the Service Employees International Union (SEIU) has trained almost 500 health care workers, including nurses, in pandemic flu preparedness with a focus on preventing respiratory exposures from all these potential sources.

According to CDC, each year, seasonal influenza is a factor in more than 36,000 deaths in the United States, and 250,000 to 500,000 deaths worldwide.[68] NIH supports research to develop more effective diagnostics, treatments, and preventive measures for seasonal influenza. The Centers of Excellence for Influenza Research and Surveillance (CEIRS) program is expanding its animal influenza surveillance program internationally and domestically, and focuses on high-priority areas in influenza research.[69] The NIH Multinational Influenza Seasonal Mortality Study (MISMS) analyzes national and global mortality patterns associated with influenza virus circulation.[70] NIH participates in the South East Asia Infectious Diseases Clinical Research Network (SEAICRN), which helps its partners develop clinical research capacities and hosts events and training sessions to mitigate outbreaks of influenza and other emerging infectious diseases.

The Centers of Excellence for Influenza Research and Surveillance program is expanding its animal influenza surveillance program internationally and domestically, and focuses on high-priority areas in influenza research.

[63] For more information, see http://www.ncbi.nlm.nih.gov/genomes/FLU/FLU.html.
[64] For more information, see http://www3.niaid.nih.gov/topics/Flu/understandingFlu/2009h1n1.htm.
[65] For more information, see http://www.cdc.gov/H1N1flu/qa.htm.
[66] For more information, see http://www3.niaid.nih.gov/news/newsreleases/2009/H1N1pedvax.htm.
[67] For more information, see http://www3.niaid.nih.gov/news/newsreleases/2009/H1N1pregnanttrials.htm and http://www.clinicaltrials.gov/ct2/show/NCT00963430?term=NCT00963430&rank=1.
[68] For more information, see http://www.cdc.gov/flu/keyfacts.htm.
[69] For more information, see http://www3.niaid.nih.gov/topics/Flu/default.htm. Scientists associated with the CEIRS program are initiating research on the pathogenicity and transmission of 2009 H1N1, studying immune response to this novel influenza strain, and beginning preparation of a reference strain that can be used for vaccine manufacturing.
[70] Miller MA, et al. *N Engl J Med* 2009;360(25):2595-8. Epub 2009 May 7. PMID: 19423872.

Biological Countermeasures Research

The NIH biodefense research program has achieved major successes in the development of countermeasures against significant bioterror threats. Some countermeasures are stockpiled or available for emergency use; others in the development pipeline have been transferred to the HHS

Biomedical Advanced Research and Development Authority (BARDA) for advanced development. Promising candidate countermeasures in development include ST-246, a smallpox drug candidate that has protected animals from an otherwise lethal exposure to live poxviruses.[71] ST-246 has been used recently under emergency use investigational new drug (E-IND) applications to treat life-threatening complications of vaccinia exposure.[72] Advanced development and production continues for a recombinant protective antigen vaccine for anthrax and a modified vaccinia Ankara vaccine for smallpox.[73]

Advanced development and production continues for vaccines for anthrax and smallpox.

NIH supports partnerships with government, industry, small businesses, and academia to facilitate the development of vaccines and therapeutics against diseases such as botulism and anthrax, as well as against Ebola and Marburg viruses. NIH also supports the development of a nonhuman primate model for plague, which has been useful in studies of three licensed antibiotics for plague.

[71] For more information, see http://www3.niaid.nih.gov/topics/smallpox/Smallpox.htm.
[72] CID 2008:46 (15 May); (CDC). *MMWR Morb Mortal Wkly Rep* 2009;58(19):532-6.
[73] For more information, see http://www3.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/.

Chemical Countermeasures

NIH helps coordinate research to develop safe and effective medical countermeasures against chemical weapons. The NIH Countermeasures Against Chemical Threats (CounterACT) Research Network supports the development of medical countermeasures to prevent, diagnose, and treat conditions caused by chemical agents that might be used in a terrorist attack or released by industrial accidents or natural disaster. The network, a collaboration between NIH and the U.S. Department of Defense, includes Research Centers of Excellence, individual research projects, small business research grants, contracts, and other programs that conduct basic, translational, and clinical research. The network has developed therapeutics for cyanide, nerve agents, chlorine, sulfur mustard, and radiation exposures. Training of personnel remains a critical facet of effective response to a release of chemical or nuclear/radiological material. For the past 15 years NIH has worked with the SEIU to provide high-quality training for hazardous materials emergency responders.

The NIH Countermeasures Against Chemical Threats (CounterACT) Research Network supports the development of medical countermeasures to prevent, diagnose, and treat conditions caused by chemical agents that might be used in a terrorist attack or released by industrial accidents or natural disaster.

Nuclear/Radiological Countermeasures

NIH continues to lead HHS efforts to sponsor and coordinate research to develop medical countermeasures to mitigate and/or treat radiation-induced damage.[74] Many candidate medical countermeasures are in the early stages of discovery, including medical countermeasures for hematopoietic acute radiation syndrome (ARS), gastrointestinal ARS, radiation-induced lung pneumonitis and/or fibrosis, and other radiation-induced injuries. Three orally bioavailable forms of diethylenetriaminepentaacetic acid (DTPA) for treating victims with internal radionuclide contamination

from fallout, or “dirty bombs,” are in development. Other areas of research include characterization of genomic, proteomic, metabolomic, and cytogenetic markers of radiation injury, and development of biodosimetry devices to provide accurate and timely radiation exposure information to assist in medical triage and treatment strategies.[75]

[74]For more information, see http://www3.niaid.nih.gov/topics/radnuc/
[75]For more information, see http://www3.niaid.nih.gov/topics/radnuc/.

Infrastructure and Research Resources

NIH has invested substantially in the intellectual and physical infrastructure needed to build the Nation’s capacity for research on biodefense and emerging infectious diseases.[76] The NIH-funded 11 Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research are developing new or improved ways to treat, diagnose, and prevent illnesses including anthrax, plague, and dengue fever. NIH has supported the construction of two National Biocontainment Laboratories. Thirteen NIH-funded Regional Biocontainment Laboratories have BSL-3 capacity.

NIH also supports research resources including databases and data integration services. For example, NIH maintains the Influenza Virus Resource, a database of influenza viral genome sequences that enables researchers worldwide to compare different virus strains, identify genetic factors that determine their virulence, and identify new therapeutic, diagnostic, and vaccine targets.[77] In the spring of 2009, with the rapid emergence of the 2009 H1N1 pandemic, the database received more than 2,200 influenza sequences from CDC and laboratories from 35 countries.

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[76] For more information, see http://www3.niaid.nih.gov/LabsAndResources/resources/rce/default.htm and http://www3.niaid.nih.gov/news/newsreleases/2009/RCEs_ARRA.htm.
[77] For more information, see http://www.ncbi.nlm.nih.gov/genomes/FLU/FLU.html.

International Collaboration

Controlling infectious diseases not only saves lives but is essential for building a strong global economy and maintaining international stability. NIH participates in efforts including the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR), the Global Fund to Fight AIDS, Tuberculosis, and Malaria, and other global initiatives. NIH supports networks of U.S. and international scientists, trains U.S. and foreign investigators to work internationally, and enhances basic biomedical, clinical, and behavioral research capacity and facilities around the world. Partnerships, including those with bilateral and multilateral international partners, industry, and host governments, provide extraordinary opportunities for research on vaccines, drugs, and new diagnostics to benefit local populations where the research is done.

Over the last decade, NIH has expanded significantly its portfolio of international biomedical research

and its global collaborations and partnerships. NIH international infectious disease research includes:

- Studies of HIV/AIDS and maternity care in Kenya
- Studies of heterosexually transmitted HIV infections among couples in urban Zambia and Rwanda
- Use of task shifting—delegating tasks, where appropriate, to less specialized health workers—to effect scale-up of HIV treatment services in Zambia
- Human Papillomavirus (HPV) vaccine trials in Costa Rica that validated the ability of virus-like particle vaccines to protect against HPV 16/18 infection[78]
- Assessments of long-term antibiotic treatment for *Chlamydia trachomatis*, a leading cause of blindness in the developing world, through a clinical trial in Ethiopia

Over the last decade, NIH has expanded significantly its portfolio of international biomedical research and its global collaborations and partnerships.

Other NIH international collaborations include the Project Phidisa clinical research project on HIV/AIDS in South Africa, and the NIH International Centers for Excellence in Research (ICER) sites in Mali, Uganda, and India. The ICERs conduct sustained research on malaria, HIV/AIDS, HIV and TB co-infections, and other diseases in areas that bear the highest infectious disease burden.

[78] For more information, see http://clinicaltrials.gov/ct2/show/NCT00867464.

Notable Examples of NIH Activity

Key

E = Supported through **E**xtramural research
I = Supported through **I**ntramural research
O = **O**ther (e.g., policy, planning, or communication)
COE = Supported via congressionally mandated **C**enter **o**f **E**xcellence program
GPRA Goal = **G**overnment **P**erformance and **R**esults **A**ct
ARRA = **A**merican **R**ecovery and **R**einvestment **A**ct

IC acronyms in **bold** face indicate lead IC(s).

Basic Research

Solving One of Immunity's Puzzles: NIH scientists recently identified a protein required for the crucial interactions between T and B cells that lead to production of antibodies and long-lasting immunity to infectious diseases. T cells and B cells interact to form cellular centers, where B cells proliferate and produce antibodies to fight off invading microbes. This process is crucial to normal immune function and resistance to infectious disease. Researchers demonstrated that a protein, SAP, mediates interactions between T and B cells. Specifically, the team found that T cells lacking SAP do not bind strongly to the B cells they would otherwise recognize. This in turn prevents B cells from receiving crucial signals they need to help build antibody-secreting cells. This malfunction leads to the poor immune response observed in patients with X-linked lymphoproliferative disease, a rare disorder

affecting newborn boys.

- Qi H, et al. *Nature* 2008;455(7214):764-9. PMID: 18843362. PMCID: PMC2652134.
- For more information, see http://www.genome.gov/27528397
- This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- (E, I) (**NHGRI, NIAID**)

New Program to Focus on Better Defining Human Immune Profiles: In 2009, NIH requested applications for a new research program designed to build on recent advances in immune profiling to measure the diversity of human immune responses to infection or vaccination. Grantees will use a variety of modern analytical tools that will define molecular signatures of specific infections, vaccines, or immune adjuvants, as well as describe steady-state human immune status by a number of parameters. This program is a critical component of the NIH immunology research portfolio. This initiative supports studies that characterize human immune cells and their products isolated from diverse subsets of the population after vaccination, infection, or treatment with adjuvants. NIH will create a grantee consortium that will develop and manage a comprehensive database that consolidates and disseminates information for the scientific community and develop new assays and bioinformatics tools to facilitate productivity. This program, originally intended as an FY 2011 initiative, began 1 year early with ARRA funding.

- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-09-040.html
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Molecular Biology and Basic Research*
- (E) (**NIAID**) (ARRA)

Microbial Genomics: NIH has made significant investments in large-scale, whole-genome sequencing of pathogens over the last decade. NIH also provides comprehensive genomic, bioinformatic, and proteomic resources and reagents to the scientific community:

- The NIH Genome Sequencing Centers of Infectious Diseases rapidly produce high-quality genome sequences of human pathogens and invertebrate vectors of diseases. Over the last decade, NIH has supported large-scale, whole-genome sequencing of pathogens and vectors. Thousands of bacteria, fungi, parasites, invertebrate vectors of diseases, and viruses have been sequenced, including pathogens that cause anthrax, influenza, aspergillosis, TB, gonorrhea, chlamydia, and cholera. For example, more than 3,733 human and avian influenza isolates have been sequenced including almost 500 for H1N1 (as of December 2009).
- The Pathogen Functional Genomics Resource Center generates and distributes genomic data sets, reagents, resources, bioinformatic analysis tools, and technologies for functional analysis of pathogens and vectors.
- Clinical Proteomics Centers for Infectious Diseases and Biodefense apply state-of-the art proteomics technologies for the discovery, quantification, and verification of protein biomarkers in infectious diseases. These data are released to the scientific community and may aid in the production of vaccines, diagnostics, and therapeutics.
- Systems Biology Centers for Infectious Diseases bring together a diverse group of scientists to analyze, identify, quantify, model, and predict the overall dynamics of microbial organisms' molecular networks and their host interactions using both computational and experimental methodologies.

- For more information, see http://www3.niaid.nih.gov/topics/pathogenGenomics/default.htm
- This example also appears in Chapter 3: *Genomics*

- (E/I) (**NIAID**)

Vaccine Research: NIH scientists developed innovative technology that enabled vaccines to virtually eliminate *Haemophilus influenzae* type B meningitis as the leading cause of acquired intellectual disability in the United States. Researchers now are applying this technology to develop a malaria vaccine that prompts an individual's immune system to eliminate the infectious malaria parasite, Plasmodium, from mosquitoes. Using more conventional methods, NIH scientists are testing a new anthrax vaccine made with a purified protein. This vaccine will enable researchers to measure and determine the minimum level of protein needed to confer protection and minimize side effects, compared to the existing anthrax vaccine.

- (I) (**NICHD**, NIAID, NIDDK)

Antimicrobial and Prebiotic Activity of Oligosaccharides: After lipids and galactose, oligosaccharides comprise the third most prevalent component of human milk. Oligosaccharides are composed of sugar molecules, linked together in short chains in hundreds of combinations. However, oligosaccharides are non-nutritive for human infants. Evidence is accumulating that the reason for the evolutionary persistence of large amounts of oligosaccharides in human milk is because of their antimicrobial properties. These findings appear to signal the advent of a new class of antimicrobial agents that could be used to prevent bacterial and viral infections of the gastrointestinal tract.
NIH now is supporting research to shed light on how oligosaccharides can prevent enteric infections and to use oligosaccharides to help prevent or treat infections. A key step in reaching this goal is to develop biosynthetic means of producing large enough quantities of oligosaccharides with antimicrobial properties for preclinical tolerance and safety studies and for safety and clinical testing in populations that are exposed to gastrointestinal pathogens.

- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-08-004.html
- (E) (**NICHD**)

Tackling Neglected Tropical Diseases: Neglected tropical diseases (NTDs) such as lymphatic filariasis, schistosomiasis, leishmaniasis, and dengue take a tremendous toll on global health. The World Health Organization estimates that more than 1 billion people—approximately one-sixth of the world's population—suffer from at least 1 NTD. NIH scientists and NIH-supported researchers in countries where NTDs are widespread are developing vaccines and treatments for diseases such as leishmaniasis and identifying new drugs for sleeping sickness and Chagas' disease. NIH-supported researchers also have made a significant leap forward in the battle against schistosomiasis by identifying potential new therapies through the use of genomics and medicinal chemistry. The Vector Biology Research Program supports research on several vectors that transmit agents of NTDs. Through this program, a project in French Polynesia aims to reduce populations of *Aedes polynesiensis*, a mosquito species responsible for spreading filariasis. Other investigators studying the mosquito immune response against filarial worms hope to identify targets for blocking development of the worm inside the mosquito. NIH scientists studying the salivary proteome of NTD vectors are identifying novel biologically active compounds and vaccine targets. In FY 2009, NIH-supported researchers reported the first complete genome sequences for two parasite species that cause schistosomiasis. Finally, a public-private partnerships for product development program is designed to accelerate research and development of new diagnostic, preventive, therapeutic, and control strategies for infectious diseases of global importance for which commercial markets currently provide

insufficient incentive for corporate investment.

- For more information, see http://www3.niaid.nih.gov/topics/tropicalDiseases/default.htm
- For more information, see http://www3.niaid.nih.gov/news/newsreleases/2009/schisto_genomes.htm
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E/I) (**NIAID**)

Bone Marrow Stromal Cells Help Fight Sepsis: Sepsis is a serious medical condition that affects 18 million people per year worldwide, and is characterized by a generalized inflammatory state caused by bacterial infection. Widespread activation of inflammation and blood clotting pathways leads to multiple organ failure, collapse of the circulatory system (septic shock), and death. In the last few years, it has been discovered that bone marrow stromal cells (BMSCs, also known as mesenchymal stem cells) are potent modulators of immune responses. In this study, BMSCs were administered before or shortly after inducing sepsis by puncturing the intestine to determine whether BMSCs injected into the circulation would have a beneficial effect in preventing or attenuating septic shock. Infusion of BMSCs significantly decreased sepsis-induced mortality and increased organ function in an animal model. The effects appear to be mediated by the production of Prostaglandin E2 when BMSCs are activated during the early stages of sepsis. Prostaglandin E2 subsequently induces the recipient's macrophages to produce substantially more IL-10, a factor that dampens the inflammatory response, which if left unabated, leads to death. This is the first determination of a mechanism by which BMSCs modulate the immune response in an animal model of sepsis. As many people die of sepsis annually as die from heart attacks. A new treatment or preventative regimen desperately is needed. Since the animal model suggests that the BMSCs need not be isolated from the same individual as will receive them, it is possible that cells isolated from nonrelated donors could be prepared and stored for use in patients with high risk for sepsis.

- Nemeth K, et al. *Nat Med* 2009;15(1):42-9, PMID: 19098906. PMCID: PMC2706487.
- For more information, see http://www.nature.com/nm/journal/v15/n1/abs/nm.1905.html
- This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
- (I) (**NIDCR**)

Metabolic Network Model of a Human Oral Pathogen: The bacterium *Porphyromonas gingivalis* causes severe, chronic periodontal disease. Recently NIH-supported researchers constructed a complex metabolic network map for *P. gingivalis* with which to model the metabolic properties of all genomically identified components of the system. The scientists used a technique known as flux-balance analysis (FBA) to construct the model, which consisted of 679 metabolic reactions involving 564 metabolites. There was significant correlation between the model's predictions and the bacterium's experimentally observed metabolism. The true power of this model became apparent when "virtual knockouts" were employed to predict the effect of the loss of certain genes or metabolic pathways on growth rate, and the model very effectively predicted disturbances affecting biosynthesis of large molecules known as lipopolysaccharides. This is the first description of a model of this type for an oral periodontal pathogen. Still in their infancy, metabolic network models are a logical extension of genome sequence data. They can provide the ability to perform virtual metabolic modeling of organisms with limited or no in vivo experimental histories. These models also could be applied to highly interdependent mixed microbial communities, including the oral microbiome, ultimately resulting in new biomedical applications. Such modeling greatly increases opportunities to

discover new antibacterial drug targets. These studies provide new molecular targets for therapeutic drugs; they also can suggest the molecular mechanisms for virulence, intracellular persistence and survival, and ability of the bacteria to survive stresses from the (in this case, human) host defense mechanisms.

- Mazumdar V, et al. *J Bacteriol* 2009;191(1):74-90. PMID: 18931137. PMCID: PMC2612419.
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Technology Development*
- (E) (**NIDCR**)

Major Infectious Diseases

Transforming TB Research: Diagnosis, treatment, and control of tuberculosis (TB) increasingly are complicated by the HIV/AIDS co-epidemic and the emergence of multidrug-resistant (MDR) TB and extensively drug-resistant (XDR) TB. NIH is pursuing six critical areas for additional investigation: (1) new TB diagnostic tools; (2) improved therapies for all forms of TB; (3) basic biology and immunology of TB; (4) MDR TB and XDR TB epidemiology; (5) clinical management of MDR TB and XDR TB in people with and without HIV infection, including children; and (6) TB prevention, including vaccines. Recent NIH advances in TB research include:

- Two FDA-approved drugs are found to work in tandem to kill laboratory models of *Mycobacterium tuberculosis* (Mtb) strains, the bacterium that causes TB. The drugs—meropenem and clavulanate—are used to treat other bacterial diseases. A clinical trial is being developed to test the combination in people who have XDR TB.
- New information on the pharmacology of existing and new anti-TB compounds may facilitate the development of improved treatment regimens for adults and children.
- Clinical trials have shown that the immune systems of children who are HIV-infected do not respond well to the current TB vaccine, BCG.
- Clinical trials also have shown that mortality among TB patients co-infected with HIV is reduced drastically when antiretroviral therapy is provided at the same time as TB therapy. Additional studies are underway to determine optimal strategies for the prevention, treatment, and diagnosis of TB in the setting of HIV infection.

Several NIH-supported academic institutions, public-private partnerships, and commercial entities are developing rapid tests for early detection of all forms of TB, including MDR and XDR TB.

- For more information, see http://www3.niaid.nih.gov/topics/tuberculosis
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E/I) (**NIAID**)

Development and Testing of Malaria Vaccines and Therapeutics: NIH supports recent calls to work toward the goal of malaria eradication. Means toward this end include stopping the spread of the malaria parasite, reducing the burden of disease region by region, and eliminating the parasite from malaria-endemic countries and then from every country throughout the world. In FY 2008, NIH assessed its malaria research portfolio and identified opportunities for the next phase of malaria research. This led to the publication of the Strategic Plan for Malaria Research and the related NIAID Research Agenda for Malaria. NIH recently launched a new initiative, the International Centers of

Excellence in Malaria Research, to support a novel, global, multidisciplinary approach to understanding malaria in the evolving context of control, elimination, and eradication. NIH researchers recently began clinical investigations to assess malaria biology and pathogenesis with collaborators in Mali and Cambodia, activities that resulted in the completion (or expansion) of research facilities and hospitals to support new malaria research programs. Examples of NIH-supported advances in malaria research include:

- Successfully decoding the genome of the parasite that causes relapsing malaria and determining that the anti-malarial drug, chloroquine, may once again be used to prevent malaria in African children.
- Investigating novel vaccine strategies, such as those that block transmission of the malaria parasite to the mosquito vector, and exploring the molecular biology of the parasite and its interaction with humans.

Ten vaccine candidates currently are in preclinical development and five are in clinical trials.

- For more information, see http://www3.niaid.nih.gov/topics/Malaria/
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E/I) (**NIAID**)

Guidelines for the Medical Management of HIV: HHS issues Federal guidelines for the medical management of HIV infection and its associated co-infections, including antiretroviral treatment of HIV disease, prevention and treatment of opportunistic infections, and prevention of mother-to-child transmission of HIV. The guidelines are written, reviewed, and updated by working groups of the NIH OAR Advisory Council made up of HIV experts from across the country, including physicians, pharmacists, researchers, and community representatives. The guidelines represent the state of knowledge regarding the medical management of HIV disease in the United States. As the introduction and/or availability of new therapeutic agents, new clinical data, and emerging disease threats may change therapeutic options and preferences rapidly, the guidelines are updated frequently and are available as a "living document" on the AIDS*info* website. Updates that recently were added to the AIDS*info* website include the *FDA Alert: Use of Antivirals Tamiflu and Relenza in Children* and the *CDC Interim Guidance-HIV-Infected Adults and Adolescents: Considerations for Clinicians Regarding Novel Influenza A (H1N1) Virus*.

- This example also appears in Chapter 3: Health Communication and Information Campaigns and Clearinghouses
- (O) (**OAR**)

HIV Topical Microbicides: Topical microbicides are small molecule prophylactic treatments to prevent the transmission and spread of HIV. Guided by the NIAID Topical Microbicide Strategic Plan, NIH is funding a number of microbicide research studies through the Microbicide Trials Network (MTN), the HIV Prevention Trials Network (HPTN), and the Microbicide Innovation Program (MIP). The microbicides under investigation are designed to prevent HIV transmission by killing or inactivating microbial pathogens, strengthening the body's normal defenses, blocking attachment of HIV to susceptible cells, and preventing HIV from spreading to other uninfected cells.
Microbicides typically are administered via a gel, foam, or cream intended to prevent the sexual transmission of HIV and other sexually transmitted infections when applied topically inside the vagina or rectum. In February 2009, NIH-supported researchers found that an investigational vaginal gel

called PRO 2000, intended to prevent HIV infection in women, is safe and approximately 30 percent effective (33 percent effectiveness would have been considered statistically significant). While additional data are needed to determine if PRO 2000 protects women from HIV infection, it was the first human clinical study to suggest that a microbicide may prevent male-to-female sexual transmission of HIV infection.

- For more information, see http://www3.niaid.nih.gov/topics/HIVAIDS/Research/prevention/research/Microbicides/research.htm
- For more information, see http://www3.niaid.nih.gov/news/newsreleases/2009/HPTN_035_gel.htm
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (**NIAID**, NICHD, NIMH)

HIV/AIDS Epidemiological and Long-Term Cohort Studies: NIH continues its support of the largest HIV/AIDS observational studies in the United States, the Women's Interagency HIV Study (WIHS) and the Multicenter AIDS Cohort Study (MACS) of homosexual and bisexual men. These studies repeatedly have made major contributions to our understanding of HIV transmission, disease progression, and best treatment practices. The WIHS, now in its 16th year of research, studies the natural history of HIV infection and AIDS progression in 2,404 HIV-infected and uninfected women, and bridges the gap between theoretic benefits and sustainable gains of antiretroviral therapy. The MACS, now in its 26th year of research, studies the natural history of HIV infection and AIDS progression in 6,973 homosexual and bisexual men at sites located in Baltimore, Chicago, Pittsburgh, and Los Angeles. These domestic cohorts are on the forefront of research to define the clinical manifestations of long-term HIV/AIDS infection. Data from these cohorts have resulted in published studies on the long-term risk of HIV/AIDS on cardiovascular disease. Studies have been initiated on aging, sleep disorders, frailty, renal function, cognitive function, and behavior among HIV-infected persons.

- For more information, see http://www3.niaid.nih.gov/about/organization/daids/daidsepi.htm
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (**NIAID**, NCI, NCRR, NICHD, NIDA)

Intervention Reduces Risky Sexual Behavior Among Homeless HIV-Infected Adults: HIV infection in the United States is found more commonly among populations with significant life stressors, such as homelessness and drug use. An NIH-funded program (the Healthy Living Program) already shown to reduce risky sexual and substance abuse behavior among HIV-infected adults also appears to be effective in improving the lives of HIV-infected homeless or near-homeless adults. The program consisted of three intervention modules of five sessions each, designed to help participants reduce risky sexual behaviors and drug use, improve their quality of life, and sustain healthy behaviors. Compared with a control group who did not receive the Healthy Living Program intervention, individuals who were homeless or near-homeless in the 3 years prior to and during the study and who participated in the intervention engaged in 34 percent fewer risky sexual acts and 72 percent fewer sexual encounters with partners who were not infected with HIV or were of unknown HIV status. The study's results highlight the importance of programs designed to prevent or reduce the spread of HIV among people in high-risk populations. They also indicate that intervention programs focusing on skills development and including the physical and mental health needs of participants, are

more likely to succeed than programs focusing only on reducing HIV transmission.

- Rotheram-Borus MJ, et al. *Am J Public Health* 2009;99(6):1100-7. PMID: 18799777. PMCID: 2679793.
- For more information, see http://www.nimh.nih.gov/science-news/2008/intervention-helps-reduce-risky-sexual-behavior-among-homeless-hiv-positive-adults.shtml
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (**NIMH**)

OAR Management and Coordination of the Trans-NIH HIV/AIDS Research Portfolio and Budget: NIH supports a comprehensive program of basic and clinical biomedical and behavioral research on HIV infection and its associated comorbidities, co-infections, opportunistic infections, malignancies, and other complications. OAR plans and coordinates all NIH AIDS research, including formulation of the NIH AIDS research budget. Through its unique, trans-NIH planning, budgeting, and portfolio assessment processes, OAR ensures that NIH AIDS research dollars are invested in the highest priority areas of scientific opportunity. Each year, OAR develops the *Trans-NIH Plan for HIV-Related Research* in collaboration with scientists from NIH, other government agencies, academia, and foundations, as well as community representatives. During the process, the state of the science is reviewed, newly emerged and critical public health needs are assessed, and scientific opportunities are identified. The Plan serves as the framework for developing the annual AIDS research budget for each IC, determining the use of AIDS-designated dollars, and tracking and monitoring all NIH AIDS and AIDS-related research expenditures. The trans-NIH AIDS research budget, developed by the OAR Director in conjunction with the ICs, is explicitly tied to the objectives of the Plan. This process reduces redundancy, promotes harmonization, and assures cross-Institute collaboration. OAR also is required to prepare an annual Presidential bypass budget based solely on scientific opportunities.

- (O) (**OAR**)

OAR Management and Coordination of Trans-NIH HIV/AIDS Research to Address the AIDS Epidemic in the United States: Every nine and a half minutes, someone in the United States is infected with HIV. It is estimated that in 2006, 56,300 people were newly infected with the virus. There are large disparities in the prevalence of HIV among different racial and ethnic populations. Black men and women, Hispanic men, and men who have sex with men of all races are impacted disproportionately by HIV. In 2006, blacks accounted for 45 percent of new infections and Hispanics for 17 percent, even though those populations comprised only 13 percent and 15 percent, respectively, of the U.S. population at that time. Moreover, the prevalence rate for black men was six times the rate for white men, and the rate for Hispanic men was more than twice that for white men. OAR leads the trans-NIH planning and coordination efforts in the area of AIDS research in racial and ethnic populations. A section of the annual Trans-NIH Plan for HIV-Related Research is specifically dedicated to research in this area. The Plan, developed in collaboration with scientific experts and community members, serves as a roadmap for the planning of AIDS-related research in this area. OAR also supports a multifaceted initiative to address the U.S. epidemic, particularly in racial and ethnic populations. For example, OAR has launched a new initiative to address the serious and complex AIDS epidemic in U.S. Hispanic populations through community outreach, regional workshops, leadership development, and research collaborations. In addition, OAR, in collaboration with NIAID and the NIH CC, has provided key support for a new trans-NIH initiative on AIDS in the District of Columbia, a city with large black and Hispanic populations and where 3 percent of the

population is known to be infected with HIV.

- Centers for Disease Control and Prevention. HIV/AIDS Surveillance Report, 2007. Vol. 19. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2009. Available at www.cdc.gov/hiv/topics/surveillance/resources/reports/. Accessed July 14, 2009. Centers for Disease Control and Prevention. HIV Prevalence Estimates—United States, 2006. MMRW. 2008; 57(39);1073-1076. Available at www.cdc.gov/mmwr/preview/mmwrhtml/mm5739a2.htm. Accessed July 14, 2009.
- For more information, see http://www.oar.nih.gov/strategicplan/fy2010/pdf/Chapter5.pdf
- For more information, see http://www.nineandahalfminutes.org
- This example also appears in Chapter 2: *Minority Health and Health Disparities*
- (O) (**OAR**)

OAR-Sponsored Initiatives Targeting Scientific Needs in AIDS Research: OAR, located within the NIH Office of the Director, identifies scientific areas that require focused attention and manages and facilitates multi-Institute and trans-NIH activities to address those needs. OAR fosters this research through a number of mechanisms, such as designating funds and supplements to jump-start or pilot program areas, and sponsoring reviews or evaluations of scientific programs. OAR, alone or in collaboration with NIH ICs, also frequently convenes scientific workshops and conferences, bringing together leading researchers from around the world to review the state-of-the-science and recommend new cutting-edge initiatives. The success of these initiatives is the expansion and/or realignment of the research portfolio in targeted areas. In addition, OAR convenes meetings of the OAR Advisory Council to focus on critical scientific research areas to highlight current trans-NIH efforts and seek advice and guidance on new avenues or approaches to move the science forward. Areas recently addressed by OAR include microbicides, nutrition and the clinical management of HIV/AIDS, genomics and the host response to HIV, human immunology, the domestic AIDS epidemic, and HIV-prevention interventions for women.

- (O) (**OAR**)

Recruiting for HIV Research Using Mobile Vaccine Units: Evaluating the safety of candidate vaccines and treatments in humans depends on trust and partnership among scientists, clinicians, and study volunteers. NIH is reaching out to District of Columbia (DC)-area communities to raise awareness among diverse groups about HIV/AIDS. The mobile clinic is an extension of the vaccine clinic of the NIH Vaccine Research Center (VRC). The mobile clinic facilitates collaboration among scientists, clinicians, and study volunteers by raising awareness about HIV vaccines and by improving access for volunteers. With its new mobile clinic, the VRC enhances this vital collaboration by improving access for people in the DC metropolitan area who volunteer for clinical research studies to help find vaccines for HIV/AIDS and other infectious diseases. The mobile clinic can expand NIH outreach and recruitment efforts to neighborhoods in Baltimore and Frederick, Maryland, as well as DC and its suburban neighbors. The unit made its first community appearance in June 15, 2008, at the 33rd annual Capital Pride Festival (a signature event held by the lesbian/gay/bisexual/transgender community).

- For more information, see http://nihrecord.od.nih.gov/newsletters/2008/07_25_2008/story4.htm
- This example also appears in Chapter 3: *Clinical and Translational Research*

- (I) (**NIAID**)

Renewed Focus on Basic HIV Vaccine Discovery Research: In March 2008, NIH sponsored a Summit on HIV Vaccine Research and Development. Participants reached consensus that NIH should increase its emphasis on basic vaccine discovery research. Toward this end, the Highly Innovative Tactics to Interrupt Transmission of HIV program was established to stimulate research on novel, unconventional, "outside the box," high-risk, high-potential, and high-impact approaches that might provide long-term protection from HIV acquisition. The Basic HIV Discovery Research initiative also was initiated to support generation of knowledge that will inform new conceptual approaches to HIV vaccine design. NIH also funds new research through the B Cell Immunology for Protective HIV-1 Vaccine program to foster fundamental research on B cell immunology to derive new understanding and approaches for development of HIV vaccines. NIH continues to conduct clinical research as appropriate and seeks to answer basic research questions through clinical trials. NIH recently launched an exploratory clinical trial through the HIV Vaccine Trials Network to examine whether a two-part vaccine regimen can decrease viral load in vaccinated male study participants who later become infected with HIV. It is hoped that this study will answer important scientific questions that could lead to the discovery and development of new and improved HIV vaccine candidates.

- For more information, see http://www3.niaid.nih.gov/topics/HIVAIDS/Research/vaccines/research/
- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-09-024.html
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (**NIAID**) (GPRA)

Support for Research on the Dissemination, Implementation, and Operation of HIV Preventive Interventions: NIH continues to support research on all aspects of HIV preventive interventions. While effective preventive interventions have been developed, there is a recognized gap between their development and their later uptake by community-level service providers. In FY 2008, NIH issued a funding opportunity announcement (FOA) to encourage research ensuring that these interventions are adopted and effectively implemented. The FOA invites applications for research projects that will enhance technology transfer, dissemination, implementation, and operational research related to evidence-based HIV preventive interventions. Staff from NIH and the Centers for Disease Control and Prevention collaborated in the development of this FOA by identifying research gaps and opportunities in these areas. Five categories of projects, in particular, were identified in which additional research activities could assist in the effective and efficient implementation of HIV preventive interventions: dissemination strategies, adoption of interventions, implementation fidelity and adaptation, intervention effectiveness, and sustainability of interventions.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-08-166.html
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (**NIMH**, CDC, NICHD, NINR)

Three-Pronged Approach to Fighting HIV: The unique and formidable challenge of combating HIV is spurring leaders in medicine and public health to consider a bold new approach to fighting it. NIH and other organizations are exploring a three-pronged approach to fight the HIV/AIDS pandemic. The first prong is pre-exposure prophylaxis (PrEP), which uses antiretroviral therapies to prevent HIV infection among people who are not infected with HIV but who are at high risk of becoming infected.

NIH currently is testing this approach in clinical trials such as the iPREX study, which is examining whether the HIV treatment Truvada can prevent HIV infection among HIV-negative men who have sex with men. The second prong is a novel approach, based on mathematical modeling, which suggests that the implementation of a universal HIV testing program and the immediate initiation of antiretroviral therapy (ART) for those individuals who test positive could dramatically reduce the number of new HIV cases within the decade. NIH now is addressing a number of critical scientific issues to determine the feasibility of this approach. Finally, NIH is strongly encouraging research to cure HIV by eliminating HIV reservoirs, pockets of undetectable latent and persistent HIV, which exist even in people on ART who have an undetectable viral load. Stopping ART treatment results in a rebound of viral load to levels seen prior to treatment. NIH has launched a new initiative to identify these reservoirs and develop techniques to eradicate them.

- Paltiel AD, et al. *Clin Infect Dis* 2009;48(6):806-15. PMID: 19193111.
  Dieffenbach CW, Fauci AS. *JAMA* 2009;301(22):2380-2. PMID: 19509386.
- For more information, see http://www.washingtonpost.com/wp-dyn/content/article/2009/04/15/AR2009041503040.html
- For more information, see http://www3.niaid.nih.gov/news/newsreleases/2009/test_treat.htm
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (**NIAID**) (ARRA)

OHARA: The Oral HIV/AIDS Research Alliance: At the vanguard of basic, translational, and clinical research to combat the oral manifestations of HIV/AIDS is the NIH-funded Oral HIV/AIDS Research Alliance (OHARA), which drives and supports novel clinical studies in the United States and internationally to improve diagnosis, treatment, and management of comorbidities of AIDS-related oral complications, including necrotizing ulcers and tumors, fulminating fungal infections, and painful viral lesions that occur in almost all 33 million people infected worldwide. Their devastating effects compromise nutrition and exacerbate immune suppression in addition to the local effects. Even since the advent of antiretroviral therapy (ART), oral complications of AIDS remain a major public health problem. Though ART alleviates some symptoms, many oral lesions need additional specific treatment and globally, only 30 percent of HIV-infected individuals for whom ART is indicated receive it. The estimated prevalence of U.S cases of HIV/AIDS in 2006 exceeded 1.1 million, while about 56,300 people were newly infected with HIV that year. In its fourth year OHARA is making significant strides for people living with HIV/AIDS. OHARA is formed by world-expert scientists and clinicians. Its success is driven by three geographically and academically separate core units that provide expertise in epidemiology, mycology, and virology, embraced by a centralized NIH management and leadership. Currently, OHARA has ramped up eight clinical studies in various phases. They include studies to assess the clinical effectiveness of diagnostic tools for HIV/AIDS-related conditions, and compare the safety and efficacy of novel treatments and preventive strategies for HIV/AIDS-related oral diseases and malignancies.

- Shiboski CH, et al. *J Oral Pathol Med* 2009;38(6):481-8. PMID: 19594839.
  Jacobson MA, et al. *PLoS One* 2009;4(4):e5277. PMID: 19381272. PMCID: PMC2667217.
- For more information, see http://aactg.org/committees/scientific/optimization-co-infection-and-co-morbidity-management/subcommittees/ohara-sub-3
- For more information, see http://www.nidcr.nih.gov/Research/DER/IntegrativeBiologyAndInfectiousDiseases/AIDSImmuno.htm
- For more information, see http://aactg.org/about-actg

- For more information, see http://www.who.int/hiv/data/en/
- For more information, see http://www.cdc.gov/hiv/topics/surveillance/basic.htm#Main
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies* and Chapter 3: *Clinical and Translational Research*
- (E) (**NIDCR**, NIAID)

Understanding HIV, TB, and Malaria Co-infection: Tuberculosis (TB) is one of the leading causes of death among people living with HIV/AIDS and one of the most common opportunistic infections they experience. HIV and TB reinforce one another: HIV activates dormant TB in a person, who then becomes infectious and able to spread the TB bacillus to others. HIV infection increases the risk of getting TB by a factor of 20 or more, according to the World Health Organization. Similarly, many HIV-positive individuals are co-infected with malaria and face poorer treatment outcomes for both diseases. Notably, malaria infection in pregnant HIV-positive patients leads to worse outcomes for both the mother and the child. NIH is increasing its focus on TB co-infection with HIV, malaria, and other pathogens. Questions addressed include when to start antiretroviral therapy (ART) in patients co-infected with HIV and TB and how best to prevent development of active TB disease in HIV-infected individuals who are receiving ART. Other studies attempt to develop new diagnostics and TB treatments for individuals co-infected with TB and HIV. In addition, several studies underway assess how best to treat women and children with HIV and either TB or malaria. Finally, the Children with HIV and Malaria Project, a prospective, longitudinal study of Ugandan children, is designed to determine if HIV increases the risk of malaria in children, whether malaria is associated with accelerated HIV disease progression, if malaria treatment has a higher failure rate in HIV-infected children in comparison with HIV-uninfected children, and whether trimethoprim-sulfamethoxazole prophylaxis increases incidence of resistant malaria. The study enrolled 300 children with more than 3 years of follow-up, and concluded in September 2009.

- For more information, see http://www3.niaid.nih.gov/topics/HIVAIDS/Research/therapeutics/intro/drug_discovery.htm
- For more information, see http://www3.niaid.nih.gov/topics/tuberculosis/
- For more information, see http://www.who.int/entity/tb/challenges/hiv/tbhivbrochure.pdf
- For more information, see http://www.unaids.org/en/policyandpractice/hivtreatment/coinfection/tb/default.asp
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*
- (E) (**NIAID**)

Microbiome of the Lung and Respiratory Tract in HIV: Research grant applications were solicited in 2009 for studies to characterize the lung and respiratory tract microbiota in HIV-infected individuals and matched HIV-uninfected controls, using molecular and high-throughput techniques to identify bacteria and other organisms, including viruses, cell-wall deficient organisms, protozoa, and fungi. The characteristics and mix of organisms populating the respiratory tract, coupled with the state of local respiratory defenses, are key factors in determining whether a person remains healthy or develops infection. HIV-infected individuals are at very high risk of developing pneumonias caused by pathogenic and opportunistic microorganisms. These respiratory infections frequently cause morbidity, and they often are life-threatening. They also may increase the rate of replication of HIV, accelerating the course of HIV disease. HIV-infected individuals often experience decreased lung function following pneumonia which is not observed in normal, HIV-uninfected populations. Furthermore, lung infections and microbial colonization are suspected in the etiology of HIV-associated emphysema and pulmonary hypertension. Lung infections also may play a role in inducing the immune reconstitution syndrome

seen in some HIV-infected patients following initiation of multidrug antiretroviral regimens. Knowledge of the role of the lung microbiome in preserving health or causing disease and the divergent effects observed in HIV-infected vs. uninfected individuals may lead to the identification of predictors of disease progression and therapeutic targets for translation into better preventive and treatment strategies.

- For more information, see http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-09-006.html
- This example also appears in Chapter 2: *Minority Health and Health Disparities*
- (E) (**NHLBI**)

Stimulating Transformative Research in HIV/AIDS: In recent years, widespread public education campaigns in the United States have fueled progress in reducing HIV/AIDS transmission that occurs through the sharing of injection equipment among drug users. However, transmission through high-risk sexual contact is on the rise—these behaviors often are exacerbated by substance abuse and ensuing altered judgment. To achieve a more comprehensive approach to this problem, NIH initiated its Avant-Garde Award series in 2008, with the goal of stimulating high-impact research from varied scientific disciplines to pave new avenues of treatment for HIV disease and prevention of new HIV infections among drug abusers. This award, modeled after NIH's Pioneer Award, provides funds of up $0.5 million per year for 5 years and uses interviews with prospective candidates to more fully discern the scientist's and project's potential. One exemplary awardee is evaluating the effectiveness of expanding highly active antiretroviral treatment (HAART) coverage among injection drug users as a population-level HIV prevention strategy. A second is focusing on the ability of HIV to hijack key proteins involved in the regulation of host cell gene expression. A second initiative, the AIDS-Science Track Award for Research Transition (A-START), facilitates the entry of newly independent and early career investigators into the area of drug abuse and HIV/AIDS, an identified area of research need. Examples of projects supported through this mechanism include research on: (1) statistical models to explain ethnic disparities in HIV/AIDS among drug users, and (2) effects of morphine on immune responses to a candidate HIV vaccine in a primate model.

- For more information, see http://www.cdc.gov/hiv/topics/surveillance/incidence.htm
- For more information, see http://www.drugabuse.gov/about/organization/arp
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (**NIDA**)

Rapid HIV Testing Clinical Trial: HIV testing is an important component of HIV prevention. To help prevent late diagnosis and HIV spread, NIH is working to identify and address the cultural barriers to making HIV screening more acceptable and to strengthen the link between education, testing and counseling, and treatment within all ethnic groups. NIH-supported modeling research has shown that routine HIV screening, even among populations with prevalence rates as low as 1 percent, is as cost-effective as screening for other conditions such as breast cancer and high blood pressure. Still, little is known about whether offering testing in the absence of counseling influences patient acceptance or how they receive results. How and whether testing absent counseling influences HIV risk behaviors among those who are HIV negative also remains to be determined. Indeed, the Institute of Medicine has recommended comparison research to include significant prevention counseling as a key variable. In this regard, a randomized controlled clinical trial—taking place in NIH's Drug Abuse Treatment Clinical Trials Network—is recruiting individuals receiving drug abuse treatment to participate in a multicenter HIV testing and counseling study. The study will assess the relative effectiveness of on-site

HIV rapid testing with brief, participant-tailored prevention counseling as compared with (1) on-site testing with information only and (2) referral for off-site HIV testing. HIV screening has important public health implications, recognized by the Centers for Disease Control and Prevention, which has called for increased HIV screening as part of its recommended guidelines. NIH is eager to advance new HIV rapid-screen technologies and counseling in community drug treatment programs and in criminal justice settings.

- For more information, see http://www.drugabuse.gov/about/organization/arp
- For more information, see http://www.drugabuse.gov/CTN/protocol/0032.html
- For more information, see http://www.drugabuse.gov/about/organization/arp
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (**NIDA**)

Multicenter AIDS Study (MACS) Small Grant Opportunity: MACS is an ongoing (since 1984) epidemiological study in several U.S. cities of multi-ethnic/racial HIV-infected and HIV-uninfected men who have sex with men (MSM). A small grant funding opportunity is enhancing the value and potential for new knowledge from the MACS by examining drug use and HIV/AIDS among MSM over the life course. Studies will include an examination of social and behavioral risk factors and trajectories, the role of drug use in neurocognitive function, and other medical consequences. Findings from these studies may lead to new insights and interventions targeting this high-risk group. Such findings reinforce the importance of implementing interventions targeting drug reduction as part of comprehensive and efficacious HIV prevention program.

- This example also appears in Chapter 3: Epidemiological and Longitudinal Studies and Chapter 3: Clinical and Translational Research
- (E) (**NIAID**, NIDA, NIMH)

Getting Proven Treatments into the Criminal Justice System: Unfortunately, most inmates in need of substance abuse treatment do not receive it while in prison and, upon their release, continue a vicious cycle of drug use and crime. In response, NIH—along with multiple Federal agencies and health and social service professionals—is working systematically to move science-based treatment interventions into the criminal justice system, where they can have a major impact. In a Delaware Work Release study, those who participated in prison-based treatment followed by aftercare were 7 times more likely to be drug free after 3 years than those who received no treatment. Other research supported under the Criminal Justice-Drug Abuse Treatment Studies (CJ-DATS) affirms the critical need for prisoners to receive effective substance abuse treatment while incarcerated and during their re-entry into the community. A recent randomized clinical trial found that prisoners who began methadone maintenance treatment in prison were significantly more likely after 12 months post-release to continue treatment and decrease drug use and criminal activity than a counseling-only group. A related issue for this population is heightened HIV risk—the U.S. prison system also being where many inmates first receive HIV testing and initiate treatment. However, only a nominal percentage continues this treatment following release. New research shows that simply providing formal assistance in filing the paperwork for antiretroviral treatment medications can promote greater continuity of HIV pharmacotherapy among released inmates. Gaining insight into ways to reduce drug use and criminal recidivism—including among adolescents for whom the same issues apply—as well as limit HIV spread in communities means huge economic and social cost savings.

- Baillargeon J, et al. *JAMA* 2009;301(8):848-57. PMID: 19244192.

Chandler RK, et al. *JAMA* 2009;301(2):183-90. PMID: 19141766. PMCID: PMC2681083.
Kinlock TW, et al. *J Subst Abuse Treat* 2009;37(3):277-85. PMID: 19339140. PMCID: PMC2803487.
Martin SS, et al. *Prison J* 1999;79(3):294-320.

- For more information, see http://www.cjdats.org/
- For more information, see http://www.drugabuse.gov/Blending/
- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Clinical and Translational Research*
- (E) (**NIDA**) (GPRA)

AIDS International Training and Research Program: The AIDS International Training and Research Program (AITRP) began in 1988 as one of the first of a new generation of research training programs sponsored by FIC. This program supports HIV/AIDS-related research training to strengthen the capacity of institutions in low- and middle-income countries (LMICs) to conduct multidisciplinary biomedical and behavioral research to address the AIDS epidemic in their countries. This program provides training for scientists from LMIC institutions to strengthen HIV-related research and public health capacities at their institutions. AITRP has trained more than 1,500 trainees. Importantly, several partnerships between AITRP programs and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) were developed in 2008 and 2009. The training provided under the AITRP program targets a cohort of scientists who benefit from the critical thinking and problem-solving skills received through research training. These skills move them forward in their careers into leadership and policymaking positions in public health in their countries. Many PEPFAR programs are directed in-country by clinician/scientists who have received FIC-supported training. This training, therefore, is an important foundation for the long-term sustainability of the PEPFAR programs. There are many successful partnerships between PEPFAR country teams and FIC AITRP grantees in Zambia, Tanzania, and Cote d'Ivoire.

- For more information, see http://www.fic.nih.gov/programs/training_grants/aitrp/
- This example also appears in Chapter 3: *Research Training and Career Development*
- (E) (**FIC**, NCI, NHLBI, NIAID, NICHD, NIDA, NIMH, OD)

Emerging Infectious Diseases and Biodefense (including seasonal and other influenzas)

Evolution of Infectious Diseases: The NIH Evolution of Infectious Diseases Program supports research on how pathogens and hosts evolve and influence each other's evolution, a critical component to understanding how new diseases emerge and spread. Research focuses on genetic changes in pathogens and hosts, evolution of immunity, the impact of vaccines and antimicrobial drugs, evolution of antimicrobial resistance, co-evolution of molecular and cellular dynamics, and the importance of environmental context. Among the diseases being studied are influenza, malaria, and dengue.

- For more information, see http://grants.nih.gov/grants/guide/pa-files/PA-07-130
- (E) (**NIGMS**)

Rapid Research Response to Emerging Disease Threats: The sudden and unpredictable emergence of infectious diseases requires advance preparation to safeguard public health. Because the groundwork of basic research can be crucial when new health threats arise, NIH conducts and

supports research to increase basic knowledge of infectious diseases, and advance development of effective diagnostics, therapeutics, and vaccines. In the case of severe acute respiratory syndrome (SARS), for instance, NIH's broad portfolio of basic research grants on coronaviruses was critical to understanding the new pathogen. NIH has developed new funding initiatives for accelerated, targeted research to encourage collaborative and product development-oriented projects. NIH also provides needed infrastructure and resources to support the research community in the event of a public health emergency. For example, the national network of Vaccine and Treatment Evaluation Units provides a ready means to conduct clinical trials to evaluate vaccines and treatments for outbreaks such as the novel 2009 H1N1 influenza. In 2009, NIH awarded new funding for 1 and renewed funding for 10 Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research (RCEs). The RCEs are a critical component of the U.S. research infrastructure for infectious diseases, and are designed to respond flexibly to changing scientific needs and priorities. RCE researchers are developing new or improved ways to treat, diagnose, or prevent illnesses, including anthrax, West Nile fever, plague, and dengue fever. The RCEs are prepared to provide scientific expertise to first responders in an infectious disease-related emergency, whether such an emergency arises naturally or through an act of bioterrorism.

- For more information, see http://www3.niaid.nih.gov/LabsAndResources/resources/rce/default.htm
- For more information, see http://www3.niaid.nih.gov/news/newsreleases/2009/RCEs_ARRA.htm
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E/I) (**NIAID**) (ARRA)

2009 H1N1—Responding to Pandemic Influenza: NIH is engaged fully in the government-wide effort to understand the 2009 H1N1 virus and rapidly develop countermeasures. Activities are being conducted in NIH-supported research networks such as the Centers of Excellence in Influenza Research and Surveillance (CEIRS) and Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases (RCEs), as well as by industry partners and individual NIH grantees. NIH used its longstanding vaccine clinical trials infrastructure—notably, the network of Vaccine and Treatment Evaluation Units—to quickly evaluate pilot lots of vaccine candidates for safety and ability to induce protective immune responses, and to determine the appropriate dose and number of dosages. Because of increased resistance to existing antiviral therapeutics, NIH is working to develop the next generation of influenza therapeutics/antivirals. Three drugs now in clinical testing include a long-acting neuraminidase inhibitor, an inhibitor of the enzyme that replicates viral genes, and a drug that prevents the virus from entering human lung cells. NIH will evaluate how well these candidate antiviral drugs block the 2009 H1N1 strain and will screen other compounds for activity against the virus. NIH also is developing diagnostic platforms that can rapidly identify a wide variety of pathogens in clinical samples, including specific subtypes of influenza. NIH is accelerating development of these platforms to provide improved diagnostics for 2009 H1N1 influenza. In addition, enrollment is complete for an NIH pandemic influenza H1N1 DNA vaccine Phase I clinical trial that has begun, and NIH scientists are conducting basic research to develop universal influenza vaccines that can protect against multiple influenza strains.

- For more information, see http://www3.niaid.nih.gov/topics/Flu/understandingFlu/2009h1n1.htm
- This example also appears in Chapter 3: *Clinical and Translational Research*

- (E/I) (**NIAID**)

Centers of Excellence for Influenza Research and Surveillance: NIH established the Centers of Excellence for Influenza Research and Surveillance (CEIRS) program in March 2007 to continue and expand its animal influenza surveillance program internationally and domestically, and to focus on several high-priority areas in influenza research. The program provides the government with information and public health tools and strategies to control and lessen the impact of epidemic influenza and the increasing threat of pandemic influenza. CEIRS activities lay the groundwork for the development of new and improved control measures for emerging and reemerging influenza viruses. Such measures include determining the prevalence of avian influenza viruses in animals in close contact with humans; understanding how influenza viruses evolve, adapt, and transmit; and identifying immunological factors that determine disease outcome. Each CEIRS site focuses on either (1) animal influenza surveillance for the rapid detection and characterization of influenza viruses with pandemic potential, or (2) pathogenesis and host response research to enhance understanding of the molecular, ecological, and/or environmental factors that influence pathogenesis, transmission, and evolution of influenza viruses; and to characterize the protective immune response. Currently, the CEIRS are responding to the 2009 H1N1 influenza outbreak by conducting research on pathogenicity and transmission of H1N1 and studying immune response to this novel influenza strain.

- For more information, see http://www3.niaid.nih.gov/topics/Flu/default.htm
- This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- (E) (**NIAID**)

Influenza Virus Resources: NIH maintains the Influenza Virus Resource, a database of influenza virus sequences that enables researchers around the world to compare different virus strains, identify genetic factors that determine the virulence of virus strains, and look for new therapeutic, diagnostic, and vaccine targets. The resource was developed using publicly accessible data from laboratories worldwide in addition to targeted sequencing programs such as NIH's Influenza Genome Sequencing Project. Updated daily, this comprehensive sequence resource includes more than 90,000 influenza sequences and more than 2,000 complete genomes. In the spring of 2009, with the rapid emergence of the 2009 H1N1 pandemic, the database received more than 2,200 influenza sequences from publicly accessible databases and included sequences from CDC and labs from 35 countries. By the end of 2009, nearly 10,000 H1N1 sequences were in the database. The combination of extensive sequence data and advanced analytic tools provided researchers worldwide immediate access for investigating the rapid spread of this flu and developing vaccines for combating it. Other influenza virus information resources also were developed in response to 2009 H1N1. To facilitate access to the scientific literature, a pre-formulated search for 2009 H1N1 papers was added to PubMed. A 2009 H1N1 Flu page with comprehensive information on Federal response, international resources, transmission, prevention, treatment, genetic makeup, and veterinary resources was added to Enviro-Health Links, which provides links to toxicology and environmental health topics of recent special interest, including information in Spanish. For the general public, patients, family members, and caregivers, a health topic on 2009 H1N1 flu, in Spanish and English, was added to the MedlinePlus consumer health resource.

- Bao Y, et al. *J Virol* 2008;82(2):596-601. PMID: 17942553. PMCID: PMC2224563.
- For more information, see http://www.ncbi.nlm.nih.gov/genomes/FLU/FLU.html
- For more information, see http://www.pubmed.gov

- For more information, see http://sis.nlm.nih.gov/enviro/swineflu.html
- For more information, see http://www.nlm.nih.gov/medlineplus/h1n1fluswineflu.html
- For more information, see http://www.nlm.nih.gov/medlineplus/spanish/h1n1fluswineflu.html
- This example also appears in Chapter 3: *Molecular Biology and Basic Research* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (I) (**NLM**)

Developing Biodefense Vaccines and Therapeutics: NIH is the lead Federal agency within HHS for conducting and supporting research on potential agents of bioterrorism and emerging infectious diseases that directly affect human health. NIAID is the lead Institute within NIH in this area. Counter measures against NIAID Category A-C priority pathogens, microbes, and toxins, which are considered to be the most significant threats to the Nation's well-being, are either nonexistent, of limited utility, or threatened by the emergence of antimicrobial resistance or intentional engineering to increase virulence or decrease drug susceptibility. Given the absence of a substantial commercial market, regulatory hurdles, and extensive clinical trial requirements, the private sector has little incentive to invest in countermeasures. To remedy this situation, NIH supports unique partnerships among government, industry, small businesses, and academia to facilitate the movement of promising products through all stages of the drug research and development pipeline, with the goal of developing vaccines and therapeutics against diseases such as smallpox and botulism, as well as for infections with Ebola, Marburg, and West Nile virus infection. NIH advances include progress toward vaccines and/or therapeutics for anthrax, smallpox, and West Nile viruses. NIH supported development of a nonhuman primate model for plague; studies in the model have been completed for three licensed antibiotics for plague. In addition, advanced development and production continues for a recombinant protective antigen vaccine for anthrax and a modified vaccinia Ankara vaccine for smallpox.

- For more information, see http://www3.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E/I) (**NIAID**)

Developing New Adjuvants to Boost Vaccine Effectiveness: Adjuvants activate the body's innate immune system, a prerequisite for effective responses by the adaptive immune system—antibody-producing B cells and antigen-specific T cells. In 2004, NIH launched the "Innate Immune Receptors and Adjuvant Discovery" initiative in response to the growing need to boost the effectiveness of vaccines against potential agents of bioterrorism and emerging infectious diseases. The initiative encouraged the discovery of novel adjuvants that stimulate the innate immune response through proteins known as pattern recognition receptors, which the innate immune system uses to identify microbial pathogens. To build on the success of this program, NIH initiated the Adjuvant Development program in 2008. Four groups were funded to advance identified adjuvants toward licensure for human use in vaccines against diseases such as influenza and tuberculosis, as well as infection with West Nile virus. The "Innate Immune Receptors and Adjuvant Discovery" initiative was reissued—inviting new grant applications—in FY 2009 to continue the generation of potential adjuvant candidates. The research focus on adjuvants yielded a major science advance in 2008 when several groups of NIH-supported investigators discovered that alum activates the innate immune system by stimulating clusters of proteins called inflammasomes, found inside certain cells. This new information should provide keys to better understanding adjuvant function and should facilitate the design of new vaccine adjuvants.

- For more information, see

http://www3.niaid.nih.gov/news/newsreleases/2008/alum_vaccine.htm
- This example also appears in Chapter 3: *Molecular Biology and Basic Research*
- (E) (**NIAID**)

Confronting the Challenge of Antimicrobial Resistance: Antimicrobial resistance has become a major public health threat that is severely jeopardizing the utility of many "first-line" antimicrobial agents. The development of resistance can be caused by many factors, including the inappropriate use of antibiotics. NIH supports a robust basic research portfolio on antimicrobial resistance, including studies of how bacteria develop and share resistance genes. NIH also is pursuing translational and clinical research in this area, including clinical studies to test interventions for community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infection and to evaluate the efficacy of off-patent antimicrobial agents. NIH laboratories are at the forefront of understanding the fundamental causes of resistance—from studies of the disease-causing organisms and the progression of disease to research on the advantages and shortcomings of current antibiotics. Specific research foci of NIH researchers and NIH-supported grantees include MRSA and vancomycin-resistant *Staphylococcus aureus* (VRSA) (commonly acquired in community settings), and drug-resistant malaria and tuberculosis. NIH supports genomic sequencing through its Microbial Sequencing Centers; researchers at these centers have sequenced the genomes of numerous disease-causing bacteria, viruses, parasites, and fungi, which may help identify mechanisms of resistance and when and where resistance emerges.

- For more information, see http://www3.niaid.nih.gov/topics/AntimicrobialResistance/default.htm
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Clinical and Translational Research*
- (E/I) (**NIAID**) (GPRA)

NIH Countermeasures Against Chemical Threats (CounterACT) Research Program: The CounterACT Research Network, as reflected in an NIH GPRA goal, develops medical countermeasures to prevent, diagnose, and treat conditions caused by chemical agents that might be used in a terrorist attack or released by industrial accidents or natural disaster. The Network, which has collaborated with the U.S. Department of Defense (DOD) from its inception in 2006, includes Research Centers of Excellence, individual research projects, small business research grants, contracts, and other programs that conduct basic, translational, and clinical research. One promising countermeasure, midazolam, which DOD researchers identified as a potential countermeasure against chemical agent-induced seizures, has entered clinical trials through the NIH Neurological Emergency Clinical Trials Network, and NIH is collaborating with DOD to complete animal studies necessary for its FDA approval as a nerve agent treatment. The New Drug Application is expected early FY 2010, with approval anticipated by the end of the year. The network also has developed six other lead compounds as therapeutics for cyanide, nerve agent, chlorine, and sulfur mustard, and has participated in pre-Investigational New Drug application meetings with FDA related to these efforts. One of the diagnostic devices developed by the program is being used in an NIH clinical trial. Three chemical agent therapeutics developed by the program also show promise as therapies for radiation exposures, and the program is collaborating with the NIH Medical Countermeasures Against Radiological and Nuclear Threats program.

- For more information, see http://www.ninds.nih.gov/research/counterterrorism/counterACT_home.htm

- For more information, see http://clinicaltrials.gov/ct2/show/NCT00809146
- For more information, see http://nett.umich.edu/nett/welcome
- This example also appears in Chapter 2: *Neuroscience and Disorders of the Nervous System* and Chapter 3: *Clinical and Translational Research*
- (E) (**NINDS**, NEI, NIAID, NIAMS, NICHD, NIEHS, NIGMS) (GPRA)

Medical Countermeasures Against Nuclear and Radiological Threats: NIH continues to lead the HHS effort to sponsor and coordinate research to develop medical countermeasures to mitigate and/or treat radiation-induced damage. Many candidate medical countermeasures are in the early stages of discovery; however, substantial effort focuses on later development as lead compounds are identified. Animal model testing is underway for 59 medical countermeasures for hematopoietic (HE) acute radiation syndrome (ARS), 18 for gastrointestinal (GI) ARS, 13 for radiation-induced lung pneumonitis and/or fibrosis, 13 for kidney injury, 7 for brain injury, and 17 for skin, including combined injuries (radiation plus burns or wounds). Three orally bioavailable forms of diethylenetriaminepentaacetic acid (DTPA), which may be used to treat victims with internal radionuclide contamination from fallout or "dirty bombs," are in development. Research into 6 lead, orally bioavailable compounds with enhanced properties for removing radioactive isotopes from the body also is ongoing. Interactions with 87 biotechnology companies through an advanced development contract have led to the identification and initial animal efficacy confirmation for 7 HE-ARS candidate medical countermeasures and 2 GI-ARS candidate medical countermeasures. Other areas of research include characterization of genomic, proteomic, metabolomic and cytogenetic markers of radiation injury, and development of biodosimetry devices to provide accurate and timely radiation exposure information to assist in medical triage and treatment strategies.

- For more information, see http://www3.niaid.nih.gov/topics/radnuc/
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (**NIAID**) (ARRA)

Infrastructure and Research Resources

Translational Research at Primate Research Centers: Nonhuman primates are critical components for translational research because of their close physiological similarities to humans. Nonhuman primates widely are used for both hypothesis-based and applied research directly related to human health, such as the development and testing of vaccines and therapies. The NIH-supported National Primate Research Centers (NPRCs) and other primate resources provide investigators with the animals, facilities, specialized assays, and expertise to perform translational research using nonhuman primates. NIH support for the centers ensures that these specialized resources are available to the research community. Several NIH ICs provide funding to investigators for specific research projects that use NPRC resources, thus increasing the efficiency of projects involving use of nonhuman primates. For example, in FY 2008, more than 1,000 research projects and more than 2,000 investigators used the animals and other resources provided by the NPRCs. Highlights of research activities include:

- Use of the simian immunodeficiency virus for AIDS-related research, including development and testing of novel microbicides to prevent infection by HIV, the virus that causes AIDS, and testing of AIDS vaccine candidates.
- Identification of the central role of specific genes and molecules in drug addiction and neurological conditions and diseases, studies of the biochemistry and physiology of drug and alcohol addiction,

and development of stem cell-based therapies for neurodegenerative diseases.

- Development of the first nonhuman primate model of a neurodegenerative disease-Huntington's disease.

    - Yang SH, et al. *Nature* 2008;452(7197):921-4. PMID: 18488016. PMCID: PMC2652570.
    - For more information, see http://www.ncrr.nih.gov/comparative_medicine/resource_directory/primates.asp
    - This example also appears in Chapter 3: *Clinical and Translational Research*
    - (E) (**NCRR**, NIA, NINDS)

Chemical Genomics: The NIH Chemical Genomics Center (NCGC), part of the NIH Roadmap for Medical Research, is an ultra high-throughput, small molecule screening center with pharmaceutical-scale power that provides state-of-the-art technologies to researchers across the United States. The center provides the translational infrastructure needed for potential drug discoveries, particularly for drugs aimed at diseases often overlooked by the private sector. For instance, schistosomiasis, also known asbilharzia or snail fever, affects an estimated 207 million people in more than 70 developing nations in tropical areas. Recently, NCGC, collaborating with NIH-funded university researchers, discovered that chemical compounds known as oxadiazoles can inhibit an enzyme vital to survival of the parasite that causes schistosomiasis. NCGC also will be a vital collaborator in a new congressionally mandated program, called Therapeutics for Rare and Neglected Diseases, which aims to encourage and speed the development of new drugs for conditions that are of relatively little interest to the pharmaceutical industry. In addition, in partnership with NIH's National Toxicology Program and the Environmental Protection Agency, NCGC is using its high-speed robotic system to screen chemicals for toxicity in cells and isolated molecular targets. This effort, known informally as the Tox21 Collaboration (for Toxicology in the 21st Century), has the potential to make crucial discoveries that will protect the public by identifying and understanding chemical toxicants to which millions of people are exposed on a regular basis, from pesticides to common household cleaners.

- Sayed AA, et al. Nat Med 2008;14(4):407-12. PMID: 18345010. PMCID: PMC2700043.
- For more information, see http://nihroadmap.nih.gov/hmp/index.asp
- For more information, see http://ncgc.nih.gov/index.html
- For more information, see http://rarediseases.info.nih.gov/TRND/
- For more information, see http://www.genome.gov/26524878
- (I) (**NHGRI, NIMH**, Common Fund - all ICs participate, NIAID, NIEHS) (GPRA)

Specialized Centers of Research (SCORs) on Sex and Gender Factors: The SCORs on Sex and Gender Factors Affecting Women's Health provide an innovative and interdisciplinary approach to advancing research on the influence of sex and gender as it relates to health and disease. Each of these SCORs emphasizes research in an area of clinical importance to women's health. The 11 current SCORs, co-funded with 5 NIH ICs and the Food and Drug Administration, address sex/gender research in the areas of depression, pain, urinary tract infection, reproductive issues, substance abuse, and osteoporosis. An example of scientific advances includes the isolation of an estrogen receptor alpha signaling process that therapeutically could be downregulated to reduce the risk for obesity and type 2 diabetes in menopausal women. In 2009, the SCORs contributed 116 journal articles, 176 abstracts, and 63 other publications (reviews and book chapters) resulting from their research.

- For more information, see http://orwh.od.nih.gov/interdisciplinary/SCORs.html
- This example also appears in Chapter 3: *Clinical and Translational Research*
- (E) (**ORWH**, FDA, NIAMS, NICHD, NIDA, NIDDK, NIMH)

New Approaches in Diagnostic Microbiology: The basic research tools developed by NIH to map the human genome form the foundation for new approaches to detect and identify infectious organisms. These techniques for sequencing the genomes of bacteria and fungi are faster and more precise than the biochemical and microscopic techniques that have been used historically in clinical laboratories to identify organisms responsible for community- and hospital-acquired infections. Additionally, collaborative work between the NIH Proteomic Research Centers and commercial companies led to the development of a complementary, novel approach for organism identification. A database of protein profiles, generated using the technique of mass spectrometry, was developed that uniquely characterizes individual species of bacteria and fungi. At NIH these genomic and proteomic techniques led to the discovery of previously unknown organisms (e.g., *Granulibacter bethesdensis*, responsible for infections in chronic granulomatous disease patients; and a currently unnamed bacterium responsible for pneumonia in a lymphoma patient), the rapid detection of *Mycobacterium tuberculosis* and other pathogens directly in clinical specimens, and the routine identification of virtually all bacteria and fungi isolated in clinical laboratories. With the development of these techniques and proof of their value, it is anticipated that other clinical microbiology laboratories will be able to adopt them for routine use.

- (I) (**CC**, NHGRI, NIAID)

International Epidemiologic Databases to Evaluate AIDS (IeDEA): The goal of the IeDEA program is to conduct analyses based on comparable data from multiple regions and studies. This initiative has established international regional centers for the collection and harmonization of data and has created an international research consortium to address unique and evolving research questions in HIV/AIDS currently unanswerable by single cohorts. High-quality data are being collected by researchers throughout the world. This initiative provides a means to establish and implement methodology to pool the collected data effectively—thus providing a cost-effective means of generating large data sets to address the high-priority research questions. Combination of data collected under various protocols frequently is very difficult and not as efficient as the collection of predetermined and standardized data elements. By developing a proactive mechanism for the collection of key variables, this initiative will enhance the quality cost effectiveness and speed of HIV/AIDS research. Participating regions include Canada and the United States, the Caribbean and Central and South America, Asia and Australia (excluding China), West Africa, Central Africa, East Africa, and Southern Africa.

- For more information, see http://www3.niaid.nih.gov/about/organization/daids/daidsepi.htm
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*
- (E) (**NIAID**, NCI, NICHD)

Adolescent Medicine Trials Network for HIV/AIDS (ATN): Although one-third to one-half of new HIV infections occur among adolescents and young adults, researchers know little about how the complex physiological changes associated with adolescence affect the transmission and course of HIV infection. NIH is supporting a national clinical research network to address the unique challenges and

clinical management needs of HIV-positive adolescents and those at risk of infection. Researchers in this network are conducting biomedical, behavioral, and community-based studies to ensure that teens can benefit from the most promising preventive and treatment interventions. For example, one recently published study conducted by the ATN documented that HIV-positive adolescents frequently do not follow prescribed treatment regimens, and the study also identified several factors associated with nonadherence to therapy.

- Rudy BJ, et al. *AIDS Patient Care STDS* 2009;(3):185-94. PMID: 19866536.
- For more information, see http://www.atnonline.org
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (E) (**NICHD**, NIDA, NIMH)

Biodefense Research Infrastructure: NIH has invested substantially in the intellectual and physical infrastructure needed to build the Nation's capacity for research on biodefense and emerging infectious diseases. This effort draws scientists from many disciplines to conduct research and development activities and to train future researchers. It also provides facilities that will greatly enhance the safe and efficient conduct of research on infectious agents. The NIH-funded infrastructure includes: (1) 11 Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research, which use a multidisciplinary approach to research and development, (2) 2 National Biocontainment Laboratories (with BSL-4 capacity, the highest level of containment), (3) 13 Regional Biocontainment Laboratories with BSL-3 capacity, and (4) services for researchers including performing medicinal and analytical chemistry, custom drug synthesis, formulation, clinical manufacturing, microbiology and virology screening, pharmacokinetics, and safety testing.

- For more information, see http://www3.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/PublicMedia/BioLabs.htm
- (E/I) (**NIAID**)

International Collaboration

The Interactions of Malnutrition and Enteric Infections: Consequences for Child Health and Development: An estimated 20 million children under 5 are severely malnourished, leaving them more vulnerable to illness and early death, according to the World Health Organization. Poor nutrition in early childhood may lead to cognitive defects and poor physical development, may increase susceptibility to and severity of infections, and may diminish the effectiveness of childhood vaccines. Focusing on the interactions between communicable and noncommunicable conditions, in 2009, the Foundation for the National Institutes of Health, together with NIH, launched a 5-year study to investigate the links between malnutrition and intestinal infections and their effects on children in the developing world. With the establishment of this remarkable public-private partnership, the project aims to shed light on critical questions related to the interaction between infections and growth and development. This large-scale, Gates-funded, NIH-led, $30 million project will support collaborative, multisite studies of malnutrition and enteric infections involving sites in Bangladesh, Brazil, India, Nepal, Pakistan, Peru, South Africa, and Tanzania. In addition to making critical discoveries that will help save the lives of the world's youngest and poorest children, the main objective of this research network is to create a standardized set of epidemiological tools to accurately study the links between intestinal infections and gut physiology as risk factors for malnutrition across a number of diverse sites

in the developing world. This research effort will be conducted in collaboration with universities in the United States and institutions in the developing world.

- For more information, see http://origem.info/malnutritionstudy/
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*
- (O) (**FIC**, FNIH)

The Multinational Influenza Seasonal Mortality Study (MISMS): The MISMS project is an international collaborative effort to analyze national and global mortality patterns associated with influenza virus circulation. MISMS aims to describe synchrony in seasonal variations of various causes of mortality associated with influenza—by state, country, and region; to describe long-term temporal trends and interannual variations in influenza mortality patterns, both within and among countries, and their association with changes in circulating subtypes of influenza virus, antigenic characteristics, population factors, and vaccine coverage; to explore the seasonal patterns and burden of influenza mortality in tropical countries; and to understand the global circulation of influenza viruses. The project highlights NIH efforts at high-level coordination within HHS and has produced numerous publications that have had important implications for global policies and approaches to influenza, most notably a June 2009, *New England Journal of Medicine* article: "The signature features of influenza pandemics—Implications for policy."

- Miller MA, et al. *N Engl J Med* 2009;360(25):2595-8. PMID: 19423872.
  Nelson MI, et al. *Virology* 2009;388(2):270-8. PMID: 19394063. PMCID: PMC2705899.
  de Mello WA, et al. *PLoS One* 2009;4(4):e5095. PMID: 19352506. PMCID: PMC2663029.
  Cattili G, et al. *PLoS One* 2009;4(3):e4842. PMID: 19290041. PMCID: PMC2653644.
  Lipsitch M, Viboud C. *Proc Natl Acad Sci U S A* 2009;106(10):3645-6. PMID: 19276125. PMCID: PMC2656132.
  Richard SA, et al. *Epidemiol Infect* 2009;137(8):1062-72. PMID: 19215637. PMCID: PMC2704924.
  Barry JM, et al. *J Infect Dis* 2008;198(10):1427-34. PMID: 18808337.
  Viboud C, Miller M. *PLoS Med* 2008;5(10):e216. PMID: 18959475. PMCID: PMC2573918.
  Nelson MI, et al. *PLoS Pathog* 2008;4(8):e1000133. PMID: 18725925. PMCID: PMC2495036.
  Miller MA, et al. *J Infect Dis* 2008;198(3):305-11. PMID: 18558871.
- For more information, see http://origem.info/misms/index.php
- (O) (**FIC**)

2009 Institute of Medicine Report, The U.S. Commitment to Global Health: Recommendations for the Public and Private Sectors: The recently released IOM report, *The U.S. Commitment to Global Health: Recommendations for the Public and Private Sectors,* reviews U.S. interest and investment in global health. This report is particularly timely and useful given the major changes in global health that have occurred since the last IOM report, *America's Vital Interest in Global Health: Protecting Our People, Enhancing Our Economy, and Advancing Our International Interests*, was released in 1997. These changes include unprecedented interest and large fiscal commitments to global health by the U.S. government and nongovernmental sectors. The IOM leveraged the contributions of 18 NIH ICs to undertake this update with additional financial support from several key private and public entities. The study makes the case for why U.S. agencies and

private sector entities should invest more heavily in global health. The report has five key recommendations that can inform NIH investments in global health in the coming years:

- Scale up existing interventions to achieve significant health gains
- Generate and share knowledge to address health problems endemic to the global poor
- Invest in people, institutions, and capacity-building with global partners
- Increase U.S. financial commitments to global health
- Set the example of engaging in respectful partnerships

The IOM panel was chaired by Dr. Harold Varmus and Ambassador Thomas Pickering. A preliminary report, titled *The U.S. Commitment to Global Health: Recommendations for the New Administration*, was released in December 2008. In May 2009, the final report, titled *The U.S. Commitment to Global Health: Recommendations for the Public and Private Sectors*, was released.

- For more information, see http://www.iom.edu/Reports/2009/The-US-Commitment-to-Global-Health-Recommendations-for-the-Public-and-Private-Sectors.aspx
- For more information, see http://www.iom.edu/Reports/2008/The-US-Commitment-to-Global-Health-Recommendations-for-the-New-Administration.aspx
- This example also appears in Chapter 2: *Cancer*, Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*
- (O) (**FIC**, NCCAM, NCI, NCRR, NEI, NHGRI, NHLBI, NIAAA, NIAID, NIAMS, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIMH, NINDS)

Inflammation, Immunology, and Cancer Virology: Several NIH programs are working to facilitate and rapidly translate advances in the discovery, development, and delivery of immunologic and antiviral approaches to improve the prevention and treatment of cancer, cancer-related viral diseases, and AIDS-associated malignancies. One notable example with implications for therapeutic cancer vaccine development is the discovery that co-delivery of Interleukin (IL)-15 with vaccines results in a more robust immune response both at the time of vaccine administration and in the event that the target antigen is encountered a second time. (IL-15 is a protein that regulates activation and proliferationn of some cells in the immune system.) IL-15 currently is in production for large-scale clinical trials. The human papillomavirus (HPV) Vaccine Trial in Costa Rica is a multiyear effort designed to test the ability of virus-like particle vaccines, originally developed at NIH, to protect against HPV16/18 infection. In addition to evaluating vaccine efficacy, the trial is examining broader measures of vaccine impact as well as immunity, natural history of HPV, and cervical neoplasia.

- Oh S, et al. *Proc Natl Acad Sci U S A* 2008;105(13):5201-6. PMID: 18362335. PMCID: PMC2278231.
- For more information, see http://ccr.nci.nih.gov
- For more information, see http://home.ccr.cacner.gov/coe/immunology/
- For more information, see https://ccrod.cancer.gov/confluence/display/CEHCV/Home
- This example also appears in Chapter 2: *Cancer*
- (E/I) (**NCI**, NIAID, OAR, ORWH)

New Insights into a Blinding Disease Prevalent in Developing World: Trachoma is a leading cause of blindness in the developing world and affects an estimated 8 million people. The disease is caused by *Chlamydia trachomatis*, a microorganism that is transmitted by flies and spreads from person to person through contact with eye discharge from infected persons. Repeated infections scar the eyelid and cause eye lashes to scrape and irreversibly damage the transparent cornea.

Trachoma occurs in overcrowded areas of extreme poverty that lack clean water and sanitation. Due to poor hygiene, specifically dirty faces, children are most likely to exchange eye discharge, making them more susceptible to trachoma. There has been considerable success in reducing trachoma in areas with moderate infection rates using the oral antibiotic azithromycin. However, in severely affected communities, infection returns rapidly after treatment. NIH-supported investigators conducted a clinical trial assessing the benefit of a longer-term, 4-course antibiotic treatment administered over 18 months to children in rural Ethiopia. Trachoma prevalence was 64 percent before treatment and dropped to less than 3 percent after treating for 6 months. However, 18 months after treatment was completed, infection rate returned to 25 percent. This study suggests that eradication must include sustainable programs that emphasize sanitation and personal hygiene and/or complete local elimination to stop the return of the disease in communities with very high prevalence.

- Lakew T, et al. *PLoS Negl Trop Dis* 2009;3(2):e376. PMID: 19190781. PMCID: PMC2632737.
- For more information, see http://www.plosntds.org/article/info%3Adoi%2F10.1371%2Fjournal.pntd.0000376
- (E) (**NEI**)

NIH Strategic Plans Pertaining to Infectious Diseases and Biodefense Research

National Institute of Allergy and Infectious Diseases (NIAID)

- *NIAID: Planning for the 21st Century — 2008 Update*
- *NIAID Research Agenda for Malaria (2008)*
- *NIAID Influenza Research: 2009 Progress Report*
- *The Research Agenda of the National Institute of Allergy and Infectious Diseases for Antimicrobial Resistance (2008)*
- *NIAID Strategic Plan for Biodefense Research (2007 update)*
- *Report of the Blue Ribbon Panel on Influenza Research (2006)*
- *NIAID Research Agenda Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis (2007)*
- *Development of Reagents for TLR and Other Innate Immune Receptors: Present Challenges — Future Directions (2007)*
- *Immunosuppression and Vaccination in Special Populations (2004)*

Special Populations

  - *Women's Health in the U.S.: Research on Health Issues Affecting Women (2004)*

National Institute of Dental and Craniofacial Research (NIDCR)

- *NIDCR Strategic Plan*
- *NIDCR Implementation Plan*

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

Branch Reports to Council with Future Scientific Directions

  - *Pediatric, Adolescent, and Maternal AIDS Branch (PAMAB), NICHD, Report to the*

NACHHD Council, June 2007

National Institute on Drug Abuse (NIDA)

- *Five-Year Strategic Plan 2009*

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

- *National Institute on Alcohol Abuse and Alcoholism Five-Year Strategic Plan, FY 08-13*

  Recommendations of the NIAAA Extramural Advisory Board (EAB)

  - *Developing an NIAAA Plan for HIV-Related Biomedical Research*

National Center for Complementary and Alternative Medicine (NCCAM)

- *Expanding Horizons of Health Care: Strategic Plan 2005-2009*

John E. Fogarty International Center (FIC)

- Pathways to Global Health Research: Strategic Plan 2008-2012

Office of AIDS Research (OAR)

- *FY 2008 Trans-NIH Plan for HIV-Related Research*
- *FY 2009 Trans-NIH Plan for HIV-Related Research*
- *FY 2010 Trans-NIH Plan for HIV-Related Research*

Other Trans-NIH Strategic Plans

- NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Radiological and Nuclear Threats
  NCI, NHLBI, NIAID, NIEHS
- NIH Strategic Plan and Research Agenda for Medical Countermeasures Against Chemical Threats
  NEI, NHLBI, NIAID, NIAMS, NIEHS, NIGMS, NINDS

Interagency Plans

- *HHS Action Plan to Prevent Healthcare-Associated Infections*
- *A Public Health Action Plan to Combat Antimicrobial Resistance*
  http://www.cdc.gov/drugresistance/actionplan/update_08.htm